

UNIVERSIDADE DE LISBOA
FACULDADE DE MEDICINA



**AUTONOMIC EVALUATION IN AFRO-DESCENDANTS PATIENTS
WITH MILD DEMENTIA
- A Pilot Study -**

André Miguel Alves de Carvalho

Supervisor: Professor Isabel Rocha
Co-supervisor: Professor Ana Valverde

Dissertation especially designed to obtain Master's degree in Neurosciences

2019

UNIVERSIDADE DE LISBOA
FACULDADE DE MEDICINA



**AUTONOMIC EVALUATION IN AFRO-DESCENDANTS PATIENTS
WITH MILD DEMENTIA
- A PILOT STUDY -**

André Miguel Alves de Carvalho

Supervisor: Professor Isabel Rocha

Co-supervisor: Professor Ana Valverde

Dissertation especially designed to obtain Master's degree in Neurosciences

2019

All statements made in this document are the sole responsibility of the author.

The printing of this dissertation was approved by *Conselho Científico (Faculdade de Medicina - Universidade de Lisboa)* at a meeting on: 11th November 2019.

“After college, I spent four years in Nigeria teaching at the University of Ibadan. I had the courage to venture into an unfamiliar world and thrive there then, as I do now. I was diagnosed April 1, 2002. And if I had been more aware of symptoms, how to live a healthier life and of the possibility of early-onset AD, I could have been diagnosed years earlier.”

[Jenny, Chicago, Ill, in People with Alzheimer stories, www.alz.org]

To Beatriz, playing and drawing...

ACKNOWLEDGEMENTS

To my supervisor and co-supervisors for their experience; ability to work and mentoring: Professor Isabel Rocha; Professor Ana Valverde and Professor Hugo Ferreira;

Special thanks to Professor Isabel Rocha for the Immediate availability, acceptance; critical spirit and dedication involved together with me in this work;

To CAFLab members (at CCUL) for technical support, training and learning: Rui Basto; Vera Geraldes; Maurício Rosa; Michele dos Santos; Ricardo Pinheiro and Sergio Laranjo;

To CERCITOP, CRL for the collaboration and especially to Neuza Marmelo for the dedication; competence and friendship;

To Neurology and Physical Medicine and Rehabilitation Service Directors of Hospital Prof. Dr. Fernando Fonseca, for the available resources for this project and its implementation;

To ACeS Sintra and ACeS Amadora chairs of the clinical councils, for meeting the research team of this project and agreed to collaborate in its disclosure and identification of potential participants;

To all my friends and hospital colleagues for believing in me, thank you very much Teresa Benzinho;

To my parents for their unconditional encouragement and my parents in law for all their family support and presence;

To Marta for being my lighthouse and an exemplary love of a lifetime...

And above all, I appreciate the informed participation of this subjects-patients and their families and caregivers, without them it would not have been possible to carry out the present study

ABSTRACT

Introduction: Data from different sources indicate that the number of people with dementia of different origins is increasing due to population ageing and improvement on diagnostic methodologies. Dementia itself doesn't discriminate between ethnicities; however, recently it was shown differences in dementia risk among ethnicities which may result from biological, behavioural, sociocultural, and environmental factors including socioeconomic determinants. In Portugal, there aren't population-based studies about the prevalence and characteristics of dementia regarding a specific race or ethnicity. In dementia, central autonomic network stations such as the hypothalamus, the amygdala, the insula and locus coeruleus are affected in its early stages. Body systems dysfunction due to dysautonomia, a failure of the autonomic nervous system, such as cardiac, urinary or thermoregulatory have been already reported in dementia investigations but studies on the integrity of the overall autonomic function in dementia has been limited and need detailed exploration, in particular in cohorts of ethnic patients as the quantification of the differences and the analysis of the involved mechanisms can aid in the development of interventions, therapeutics, and public policy to reduce and eliminate racial and ethnic differences in dementia.

Objectives: Within this pilot study, the overall purpose is to investigate autonomic function in non-caucasian afrodescendent patients with mild dementia.

Methods: Non-Caucasian afrodescendent subjects, of both sexes (n=22), aged ≥ 50 years, diagnosed with mild dementia defined in accordance to DSM criteria and after clinical diagnosis were enrolled. After anamnesis, clinical history and physical examination, autonomic function was assessed through deep-breathing, Valsalva-maneuver and hand-grip using time and time-scale methodologies. A group of caucasian subjects with the same diagnostic criteria of mild dementia aged >70 years (n=7) and a control group of afrodescendent subjects without cognitive impairment (n=12) matching age and sex were also included in the study. The participants were recruited and evaluated between February 2018 and May 2019 at the Neurology Department of Fernando Fonseca Hospital in Amadora-Sintra and with the collaboration of CERCITOP, CRL, a semi-public rehabilitation and continuing care unit in Algueirão-Sintra, during their first medical appointment regarding the complaints of cognitive decline. Participants with atrial fibrillation ablation or implantation of a pacemaker diabetes, chronic obstructive pulmonary disease, orthostatic hypotension, reflex syncope, cardiac arrhythmias, heart failure, those who had undergone cardiac surgery, those who were taken beta-blockers or several psychotropic medications such as tricyclic antidepressants, selective serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, antipsychotics and cholinesterase inhibitors or have

other significant medical causes of dementia (hypothyroidism, chronic subdural hematoma, asthma, multiple sclerosis etc.) were excluded from this study. Due to the age of the studied population some medications were allowed and included diuretics, peripheral acting calcium channel blockers, angiotensin II receptor blockers, serotonin reuptake inhibitors and benzodiazepines. Autonomic manoeuvres were evaluated using the Ewing battery analysis as well signal processing in which low frequency (LF; 0.04- 0.15Hz) and high frequency powers (HF; 15-0.4Hz) were assessed. The overall autonomic power was calculated through the relation LF/HF ($\text{mmHg}^2/\text{ms}^2$). Baroreceptor gain through the sequence method and baroreceptor efficacy were also calculated. Paired Student's T test and ANOVA "repeated measures" analysis of variance with Bonferroni's correction were applied. A value of $p < 0.05$ was considered statistically significant.

Results: Patients were divided according to their age distribution: group I: age afrodescendent subjects (AfD) of [50-70] years and group II, including two sub-groups of AfD and caucasian subjects (CA) aged >70 years. There were no significant differences between the groups of individuals in most of the factors that may potentially affect the autonomic evaluation. Systolic, diastolic arterial pressures and heart rate, at rest, were not different in all groups. Regarding autonomic evaluation, our results show that all patients have a lower autonomic tone comparing with controls. In particular, LF and HF show statistically significant differences between the groups ($p < 0.05$). Regarding general autonomic tone, there is a tendency for its decrease with age, having the AfD patients a higher tone than the CA individuals which is in line with the values of resting systolic blood pressure. The evaluation of baroreflex sensitivity or gain using the sequence method and baroreceptor effectiveness shows an impairment of baroreceptor function in all patient's groups without any significance difference between them. Regarding the autonomic manoeuvres, not all the patients were able to perform them at all while others had a deficient performance due to difficulty of communication and aging executive problems. The maneuver which was better performed was deep breathing probably because it was the first maneuver of the evaluation protocol. An additional observation is related to neuropsychology assessment to which AfD subjects present lower scores at MMSE (Group I AfD: $24,6 \pm 1,5$; Group II AfD: $23,4 \pm 1,8$); higher scores at CDR (Group I AfD: $0,7 \pm 1,3$; Group II AfD: $0,9 \pm 0,2$) and at QSM scale (Group I AfD: $10,5 \pm 5,3$) which correspond to a more pronounced cognitive and functionality impairment of AfD than CA patients.

Discussion: Both on clinics and in research, autonomic evaluation through power spectral analysis is widely used as a way to qualify and quantify autonomic function. In our study we used two different ways of evaluating autonomic testing: a time-scale analysis of a basal period and system provocative manoeuvres and we noticed that, for this population of

patients, the former was more effective in collecting autonomic information than the second. Indeed, Valsalva maneuver, deep breathing and handgrip need a high degree of motivation and cooperation from the patients which may be difficult in aged and demented patients even with mild presentations. This, leads to a strong study limitation of autonomic function with provocation in this type of patients to avoid false results, results with no consequence and a high rate of drop-outs. We also observed a reduced baroreceptor responsiveness accompanying mild dementia. In line with these results, we may hypothesize that, in our study, the baroreflex impairment is strongly related to the decrease in autonomic function but mainly in sympathetic activity, which was observed in autonomic evaluation of the basal period, the V_R and the BP changes on phase III of the Valsalva manoeuvre and the small rise of diastolic blood pressure during handgrip. However, since we worked with a reduced sample size, we need to be cautious regarding this hypothesis. Finally, another previous study suggested that baroreceptor reflex sensitivity is more sensitive to internal cognitive process during a mental task, while baroreflex effectiveness index is more sensitive to external attention process conditions. This suggestion is in line with our results, where a generalized decreased in cognitive function is associated to baroreflex impairment (both sensitivity and effectiveness) and autonomic dysfunction. Whereas baroreflex sensitivity or effectiveness may be used as marker of therapeutic efficacy is still a matter of debate but some studies already gave some hints on this possibility, because baroreflex is reduced in Alzheimer disease and is influenced by autonomic effects of cholinesterase inhibitors.

Conclusion: This pilot study is the first in Portugal addressing the autonomic function in a minority population- the afrodescendent population- suffering from mild dementia. Despite being a pilot study, our results show a pathologic pattern in the autonomic regulation in these patients evaluated through signal processing and Ewing battery of tests. The importance of these results lies on the fact that baroreflex and autonomic impairments, mainly the lack of parasympathetic reserve in dementia patients, may be related with the progression of the disease or be an inductor of co-morbidities including cardiovascular disease and orthostatic intolerance which may lead to falls, dizziness or even syncopal events in these patients. Also, baroreflex parameters may be considered as valid biomarkers of disease progression and therapeutic efficacy but further research is still needed.

Keywords: mild dementia, autonomic function, risk stratification, ethnicity, afrodescendent patients; epidemiology.

RESUMO

Introdução: Dados de diferentes fontes indicam que o número de pessoas com demência de diferentes etnias está a aumentar devido ao envelhecimento da população e à melhoria das metodologias de diagnóstico. A demência em si não discrimina entre raças ou etnias mas, recentemente, foram mostradas diferenças no risco de demência entre etnias que poderá resultar de factores biológicos, comportamentais, socioculturais e ambientais incluindo determinantes socioeconómicos. Em Portugal, não existem estudos de base populacional sobre a prevalência e características da demência em relação a uma etnia específica. Na demência, os centros cerebrais da rede autonómica central como o hipotálamo, a amígdala, a ínsula e o locus coeruleus estão afectados nas fases iniciais da demência. A disfunção autonómica traduzida por modificações dos sistemas corporais como o cardíaco, o urinário ou o termorregulatório já foi abordada em estudos anteriores de demência mas, há pouca evidência sobre a integridade da função autonómica geral nesta doença, sendo necessária investigação mais detalhada, especialmente em grupos de doentes não-caucasianos pois a quantificação das diferenças e a análise dos mecanismos nelas envolvidos ajudará nas intervenções médicas, na terapêutica e na modulação das políticas públicas no sentido da redução e/ou da eliminação das diferenças étnicas na demência.

Objetivos: Neste estudo piloto exploratório, o objectivo principal é avaliar e investigar a função autonómica de doentes afrodescendentes não-caucasianos com demência ligeira.

Métodos: Indivíduos afrodescendentes não-caucasianos (n=22), de ambos os sexos, com idade ≥ 50 anos, diagnosticados com demência ligeira de acordo com os critérios do DSM e após avaliação clínica que incluiu anamnese e exame físico, foram sujeitos a avaliação autonómica por metodologias no domínio do tempo e no tempo-escala aplicadas às variáveis fisiológicas recolhidas durante as manobras autonómicas provocatórias de respiração profunda, manobra de Valsalva e contracção isométrica. Um grupo de indivíduos caucasianos com os mesmos critérios de diagnóstico de demência ligeira (n=7) e um grupo controle de indivíduos afrodescendentes sem défice cognitivo (n=12) correspondendo em idade e sexo foram igualmente incluídos no estudo. Os participantes foram recrutados e avaliados entre fevereiro de 2018 e maio de 2019 durante uma primeira consulta médica de neurologia por queixas de declínio cognitivo, no Departamento de Neurologia do Hospital Professor Fernando Fonseca, na Amadora, Sintra com a colaboração da CERCITOP, CRL, uma unidade de reabilitação de cuidados continuados de Algueirão-Sintra. Os participantes sujeitos a ablação de fibrilhação auricular, com pacemaker; doença pulmonar obstrutiva crónica; hipotensão ortostática, síncope reflexa, arritmias cardíacas ou insuficiência cardíaca

grave, ou submetidos a cirurgia cardíaca, que tomem betabloqueadores ou medicamentos psicotrópicos como antidepressivos tricíclicos, inibidores selectivos da recaptação de serotonina-norepinefrina, antidepressivos, antipsicóticos e inibidores da acetilcolinesterase ou com outras causas médicas indutoras de demência (hipotireoidismo, hematoma subdural crónico, asma, esclerose múltipla) foram excluídos do estudo. Devido à idade da população estudada, alguns medicamentos foram permitidos e incluíram diuréticos, bloqueadores dos canais de cálcio, inibidores da enzima de conversão da angiotensina, bloqueadores dos receptores da angiotensina II, inibidores da recaptação de serotonina e benzodiazepinas. A avaliação autonómica foi efectuada no domínio do tempo através da análise de Ewing e no domínio do tempo-escala no qual a potência das baixas (LF; 0.04- 0.15Hz) e da altas frequências (HF;.15-0.4Hz) foi calculada bem como o tónus autonómico total (LF/HF; mmHg²/ms²) e o ganho e a sensibilidade do baroreflexo através do método sequencial. O teste T-Student para dados emparelhados e a análise de variância através de ANOVA com correção de Bonferroni foram usados para avaliação estatística dos resultados tendo-se considerado como estatisticamente significativo um valor de $p < 0.05$.

Resultados: Os doentes foram divididos de acordo com a sua distribuição etária: grupo I: [50-70] anos com indivíduos afrodescendentes (AfD) e grupo II: >70 anos com indivíduos AfD e caucasianos (CA). Não houve diferenças significativas entre os grupos de doentes na maioria dos factores que podem afetar potencialmente a avaliação autonómica. As pressões arteriais sistólica, diastólica e a frequência cardíaca, em repouso, não foram diferentes entre os grupos. Em relação à avaliação autonómica, estes resultados mostram que todos os doentes apresentam um tónus autonómico mais baixo em comparação aos controles. Em particular, LF e HF mostram diferenças estatisticamente significativas entre os grupos ($p < 0,05$). Em relação ao tónus autonómico geral, há uma tendência de diminuição com a idade, com os doentes AfD a terem um tónus mais alto que os CA, estando estas observações alinhadas com os valores da pressão arterial sistólica mais altos observados nos doentes AfD em repouso. A avaliação da sensibilidade ou ganho baroreflexo e sua eficácia usando o método sequencial demonstra um comprometimento da função barorreceptora em todos os grupos de doentes, sem qualquer diferença significativa entre eles. Em relação às manobras autonómicas, nem todos os participantes foram capazes de as executar eficazmente devido a dificuldades de comunicação e de coordenação psicomotora própria de doentes com idade avançada. A manobra melhor realizada foi a respiração profunda, provavelmente porque foi a primeira prova do protocolo de avaliação. Adicionalmente, observou-se que na avaliação neuropsicológica, a nível dos critérios clínicos de inclusão, ambos os grupo de doentes afrodescendentes revelaram *scores* mais baixos no MMSE (Grupo I AfD: $24,6 \pm 1,5$; Grupo II AfD: $23,4 \pm 1,8$); *scores* mais altos na CDR (Grupo I AfD: $0,7 \pm 1,3$; Grupo II AfD: $0,9 \pm 0,2$) e a

pontuação mais elevada na escala de QSM (Grupo I AfD: $10,5 \pm 5,3$) o que corresponde a um declínio cognitivo e funcional mais pronunciado, quando comparados com o grupo de doentes caucasianos.

Discussão: Tanto na clínica como na investigação, a avaliação autonómica por meio da análise espectral é amplamente utilizada para qualificar e quantificar a função autonómica. Neste estudo, utilizamos duas formas diferentes de avaliar o tónus autonómico: uma análise no domínio tempo-escala e manobras provocatórias autonómicas. Com elas, observámos que, para esta população de doentes, o primeiro era mais eficaz na recolha de informações autonómicas do que o segundo. De facto, a manobra de Valsalva, a respiração profunda e a contracção isométrica precisam de um maior grau de motivação e cooperação dos doentes, o que pode ser difícil em doentes idosos e dementes, mesmo com apresentações ligeiras dos sintomas da doença, sendo esta uma forte limitação neste tipo de estudos. Também, foi observada uma reduzida capacidade de resposta do reflexo barorreceptor nestes doentes com demência ligeira comparativamente aos controlos saudáveis. De acordo com esses resultados poderemos colocar a hipótese que, no nosso estudo, o comprometimento da resposta barorreflexa esteja fortemente relacionada com a diminuição da função autonómica simpática, como foi observado na avaliação autonómica no período basal, bem como através do atraso da manobra de Valsalva e o reduzido aumento da pressão arterial diastólica durante a prova de contracção isométrica. No entanto devido ao tamanho reduzido da amostra conseguida, teremos que ser cuidadosos na formulação desta hipótese. De referir, também, que estudos anteriores sugerem que a sensibilidade do reflexo barorreceptor é permeável ao processamento mental (interno) durante tarefas cognitivas e que o índice de eficácia barorreflexa é mais sensível a estados mentais de processamento de atenção visual externa. Estas evidências parecem estar concordantes com os nossos resultados, nos quais se verifica uma diminuição generalizada da função cognitiva associada ao comprometimento barorreflexo, quer da sensibilidade (BRS) quer da eficácia (BEI), e a disfunção autonómica. Considerando que o BRS e/ou BEI possam ser usados como biomarcadores de eficácia terapêutica é motivo de debate, embora, alguns estudos já evidenciaram resultados sobre essa possibilidade, porque o baroreflexo está reduzido na doença de Alzheimer (que origina um dos tipos de demência) e é influenciado pelos efeitos autonómicos dos inibidores da colinesterase.

Conclusão: Este estudo piloto é o primeiro em Portugal a abordar a função autonómica numa população minoritária - a população afrodescendente - com diagnóstico de demência ligeira. Apesar de ser ainda um estudo piloto exploratório, os resultados obtidos mostram um padrão patológico na regulação autonómica dos doentes avaliados através do processamento de sinal no domínio do tempo-escala e da bateria de testes de Ewing. A importância destes resultados reside no facto de que as alterações barorreflexas e

autonómicas podem estar relacionadas com a progressão da doença ou serem indutoras de comorbidades, incluindo doenças cardiovasculares e intolerância ortostática, que podem levar a quedas, tonturas ou mesmo a eventos sincopais nestes doentes. Além disso, o BRS e/ou o BEI podem ser considerados como biomarcadores válidos da progressão da doença e da eficácia terapêutica, mas são necessárias mais investigações futuras.

Palavras-chave: demência ligeira, função autonómica; estratificação de risco, etnia, doentes afrodescendentes, epidemiologia.

CONTENTS

i.	ABSTRACT	7
ii.	RESUMO	10
iii.	List of figures and Tables	16
iv.	List of abbreviations	18
v.	Funding	19
1.	INTRODUCTION	20
1.1	General Overview of Dementia	20
1.1.1	Definition of Dementia	20
1.1.2	Clinical Classification of Dementia	21
1.1.3	Epidemiology of Dementia	22
1.1.4	Diagnostic and Clinical characteristics	24
1.1.5	Clinical Assessment	25
1.1.6	Prognosis	28
1.1.7	Therapeutics approaches	30
1.1.8	Impact of Dementia on Quality of Life	31
1.1.9	Health Economics related to Dementia	33
1.2	Pathophysiology of dementia: Major Pathophysiology and Neuropathophysiological mechanisms.....	35
1.3	Dementia and Autonomic Function	36
1.4	The recruitment of vulnerable populations into research	40
2.	AIM OF THE PRESENT WORK	43
3.	METHODS	43
3.1	Ethics statement	43
3.2	Increasing project awareness to facilitate patient's recruitment	43
3.3	Study Population	44
3.4	Clinical and Neuropsychological assessment	45
3.5	Experimental protocol.....	45

3.5.1 - Autonomic evaluation	46
3.6 Data analysis	47
3.6.1 Ewing battery analyses	47
3.6.2 Cardiovascular variability	47
3.6.3 Baroreflex gain and effectiveness	48
3.7 Statistical analysis	48
4. RESULTS	50
4.1 Demographics and Neuropsychological assessment	50
4.2 Autonomic evaluation	59
4.2.1 Cardiovascular variability	59
4.2.2 Baroreceptor reflex study	62
4.2.3 Autonomic provocative manoeuvres	62
4.2.3.1 Deep Breathing test	62
4.2.3.2 Valsalva Manoeuvre	63
4.2.3.3 Hand-Grip test	64
5. DISCUSSION	66
6. CONCLUSIONS	70
6.1 Study limitations	70
7. REFERENCES	71
8. ATTACHMENTS	87
8.a Informed Consent to Participants	87
8.b <i>Clinical Dementia Rating Scale (CDR)</i>	93
8.c <i>Mini-Mental State Examination (MMSE)</i>	103
8.d <i>Subjective Memory Complaints questionnaire (QSM)</i>	104

List of figures and Tables:

Figure 1. Flow chart of the study inclusion steps	p.45
Figure 2. Timeline of the autonomic protocol showing the sequence of the performed manoeuvres	p.46
Figure 3. Comparison of LF band power, between the evaluated groups.....	p.59
Figure 4. Differences on parasympathetic tone between the patient's groups and the control.....	p.59
Figure 5. Autonomic outflow in groups of patients independently of age.....	p.60
Figure 6. Deep metronomic breathing of afrodescendent patients	p.61
Figure 7. The Valsalva maneuver performed by a patient	p.63
Figure 8. Two HG tests performed by patients	p.64

--

Table 1. Baseline demographic data for AD mild dementia and control groups: subjects aged [50-70] years	p.49
Table 2. Baseline demographic data for AD and CA mild dementia groups: patients aged >70 years	p.50
Table 3. Neuropsychological tests; Age & Education in the [50-70] years group of Afrodescendent subjects	p.51
Table 4. MMSE cognitive subdomains scores in the [50-70] years group of Afrodescendent subjects	p.51
Table 5. CDR cognitive subdomains scores in the [50-70] years group of Afrodescendent subjects	p.52
Table 6. Neuropsychological tests; Age & Education in the >70years group of Afrodescendent subjects.....	p.52
Table 7. MMSE cognitive subdomains scores in the >70 years group of Afrodescendent subjects	p.53
Table 8. CDR cognitive subdomains scores in the >70 years group of Afrodescendent subjects	p.53
Table 9. Neuropsychological tests; Age & Education in the >70 years group of Caucasian subjects.....	p.54
Table 10. MMSE cognitive subdomains scores in the >70 years group of Caucasian subjects	p.54

Table 11. <i>CDR cognitive subdomains scores in the >70 years group of Caucasian subjects</i>	p.55
Table 12. <i>Neuropsychological tests; Age & Education means scores between patients-groups</i>	p.55
Table 13 <i>MMSE cognitive subdomains means scores between patients-groups</i>	p.56
Table 14 <i>CDR cognitive subdomains means scores between patients-groups</i>	p.57
Table 15. <i>Values of overall power spectral analysis of heart rate and blood pressure variability in the evaluated group of subjects</i>	p.59
Table 16. <i>Values for BEI and BRS for all groups of patients and controls</i>	p.61

List of abbreviations

ACeS - *Health Center Grouping (at Portuguese net primary health care)*

AD - *Alzheimer Disease*

AfD – *Afrodescendent (non-caucasian) participant subject*

ANS - *Autonomic Nervous System*

BEI - *Baroreflex Effectiveness (index)*

BRS - *Baroreflex sensitivity or gain (index)*

CA - *Caucasian participant subject*

ChEI- *AcetylCholinesterase inhibitors*

CDR - *Clinical Dementia Rating Scale*

Db – *Daubechy 12 mother wavelet*

DB - *Deep Metronomic Breathing test*

dBp - *Diastolic Blood Pressure*

DGS – *Direcção Geral de Saúde (Portuguese Governmental Health entity)*

DNA - *Deoxyribonucleic Acid*

DSM - *Diagnostic and Statistical Manual of the American Psychiatric Association*

E/I - *Expiratory/Inspiratory index (related to deep breathing autonomic test)*

HF/LF - *low frequency power (LF) mmHg² / high frequency power (HF) ms²*

HFF - *Hospital Professor Doutor Fernando da Fonseca*

HIV - *Human Immunodeficiency Virus*

HRV - *Heart Rate Variability*

ICD - *International Classification of Diseases*

MCI - *Mild Cognitive Impairment*

MMSE - *Mini Mental State Examination*

MRI - *Magnetic Resonance Imaging*

NCD - *Neurocognitive Disorder*

NINCDS-ADRDA - *National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA)*

OECD - *Organization for Economic Co-operation and Development*

QSM - *Questionnaire of Subjective Memory (complain)*

sBP - *Systolic Blood Pressure*

TBI - *Traumatic Brain Injury*

UK - *United Kingdom*

USA - *United States of America*

VM - *Valsalva Maneuver test (of Autonomic Evaluation perform)*

WHO - *World Health Organization*

Funding

The present work was funded by the Cardiovascular Autonomic Function Lab of the Cardiovascular Centre of the University of Lisbon (www.caflab.eu).

1. INTRODUCTION

1.1 General Overview of Dementia

1.1.1 Definition of Dementia

Dementia rather than a specific disease should be considered as a syndrome, of a chronic or continuous nature, in which there is decline in cognitive function beyond what might be expected from normal ageing affecting memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement and leading to a reduction of the individual's ability to perform everyday activities (WHO, 2015). But also, a cognitive decrease in normal aging is expected and may increase reaction times among the healthy aged. For this reason, it is already known that the degree of intellectual competences in the elderly population is itself varied, which can lead to the misdiagnosis of dementia in individuals of poor intelligence (Gurland, 1981).

In current clinical practice the diagnosis of dementia is decided on the basis of a set of key clinical, histopathological and localization factors. According to The *Diagnostic and Statistical Manual* of the American Psychiatric Association (DSM, 2013), the diagnostic criteria for dementia are a demonstrable impairment in short-term and long-term memory; the ability of memory/cognitive impairment to interfere with work, social activities and relationships; evidence of an organic factor that is "aetiologically related" to the disturbance; and at least one of the following: *abstract thinking impairment; impaired judgement; aphasia; apraxia; agnosia* or *personality change*. But further differentiation of diagnosis can be made by considering the site and the histology of the dementia (these two factors help to determine which type of dementia the patient is exhibiting).

Histopathology is probably the criteria that is least susceptible to interpretation, because the molecular and biochemical evidence is clear-cut. Because of this, the only certain confirmation of a diagnosis of dementia can be made by autopsy or biopsy (McKhann *et al.*, 1984).

1.1.2 Clinical Classification of Dementia

The DSM lists the main clinical and behavioral symptoms that should appear in order to confirm a diagnosis of dementia and also the major diagnosable dementias. These are:

- (a) dementia of the Alzheimer type;
- (b) vascular dementia (or due to Stroke);
- (c) dementia due to Parkinson`s disease or Lewy-body dementia;
- (d) dementia due to Huntington`s disease;
- (e) dementia due to Pick`s disease or Frontotemporal dementia;
- (f) dementia due to Creutzfeldt-Jakob disease;
- (g) dementia due to HIV disease;
- (h) dementia due to head trauma (eg.: TBI);
- (i) dementia due to other general medical conditions;
- (j) substance-induce persisting dementia;
- (k) dementia due to multiple aetiologies;
- (l) dementia not otherwise specified

Different types of dementia affect different brain systems and reveal slightly different clinical symptoms. The most prevalent subtype of dementia is Alzheimer disease (AD) with more than 50% of cases and three outlined phases: pre-clinical AD when the disease is present in the brain but there are no symptoms; mild cognitive impairment (MCI) due to AD (also called prodromal AD) and dementia caused by AD. The dementia caused by AD involves memory, thinking and behavioral symptoms that impair a person`s ability to function in daily life and can be further clinically classified as *probable* (to be diagnosed when the person meets all the core clinical criteria), *possible* (to be diagnosed when there is an atypical or mixed presentation) and *probable or possible Alzheimer`s disease dementia with evidence of the Alzheimer`s disease pathological process* which is to be diagnosed when there is biomarker evidence that will increase the certainty that the presented dementia is due to Alzheimer`s disease. The AD was named after Alois Alzheimer who in 1907 reported the case of a 56-year-old patient with abnormal formations called presenile plaques tangle in her brain. She exhibited an obvious form of present dementia, to which Alzheimer gave his name. In addition to Alzheimer`s disease are other dementia subtypes, the most second common being vascular dementia (Roman *et al.*, 1993) and other types of dementia are frontotemporal dementia (Neary *et al.*, 1998) and dementia with Lewy bodies associated with Parkinsonism (McKeith *et al.*, 2006).

In general clinical practice, the degree of any subtype of dementia can be classified into *mild*; *moderate* or *severe* depending on the level of functional dependence and behavioral disturbance (MacKhann *et al.*, 1984; Nitrini *et al.*, 2005) with the *possible* or *probable* clinical diagnosis of Alzheimer`s disease according to the last revision criteria in 2007 of NINCDS-ADRDA (Dubois, 2007). All these dementia clinical criteria and its different etiologies or

subtypes for differential diagnosis can be found in the last 2011 Clinical Health Directorate General Publication (DGS, 2011) and compiled in the latest 5th DSM version (DSM-V, 2013).

1.1.3 Epidemiology of Dementia

The World Health Organization (WHO, 2015) estimates that there are 47.5 million people with dementia worldwide, up to 75.6 million by 2030 and nearly tripling by 2050 to 135.5 million. In this context, Alzheimer's disease takes a prominent place, representing about 60 to 70% of all dementia cases. In Portugal, since there is not yet a nationally updated epidemiological study that portrays the real situation of the problem, we can refer to the Alzheimer Europe (2014) data that point to about 182 thousand people with dementia. On the other hand, in the OECD (2017) Health at a Glance Report published on 10 November 2017, new data on the prevalence of dementia are presented, making Portugal the 4th country with the most cases/per thousand inhabitants.

The OECD average is 14.8 cases per thousand inhabitants. The estimates for Portugal reach over 205,000 people, and will rise to 322,000 cases by 2037. The Portuguese population over 65 years in 2009 reached 19.1%, the average life expectancy at birth was 2012 of 82.5 years for women and 77.3 years for men (INE, 2009) and the prevalence of cognitive impairment is 12.3% and 2.7% of dementia between 55 and 79 years old, being higher in elders (DGS, 2011). But specific epidemiological data in Portugal are sparse and a population-based studies about the prevalence and characteristics of dementia concerning a specific race or ethnicity that focused on clinical diagnosis coding in primary health care on a particular region, have not been conducted.

Age is the main risk factor for dementia and increase the prevalence rate. Between 65 and 69 the prevalence rate is 2%, rising to 4% between 70 and 74, 7% between 75 and 79, 12% between 80 and 84 and 20 % between 85 and 89. For people over 90 years of age, the prevalence rate is 41% (OECD, 2017).

According to the OECD (2017) report, the average number of people with dementia is 14.8 cases per thousand inhabitants and for Portugal the estimate is 19.9, which corresponds to more than 205,000 cases and until 2037 about 322 thousand cases.

As we already mentioned the most common type of dementia is Alzheimer's disease, which makes up 50% to of cases. Other common types include vascular dementia (25%), dementia with Lewy bodies (15%) and Frontotemporal dementia (WHO 2019). Less common causes

include Normal Pressure Hydrocephalus, Parkinson's disease; Syphilis; HIV and Creutzfeldt-Jakob disease (Santana *et al.*, 2015). But interesting is the fact that a very recent Portuguese study conducted by Ruano and his collaborators (2019) in a cohort of patients from the northern regions of the country suggested that the main cause of dementia in Portugal is related to vascular factors, contrary to what happens in most western European countries. They evaluated the prevalence of cognitive impairment and dementia in a sample of 730 individuals and attempted to identify their most frequent causes. The results show that about 4.5% of individuals over 55 years have mild dementia or cognitive impairment and that the most prevalent type of dementia is vascular dementia. The high incidence of stroke in Portugal is a risk factor compared to other countries, which may explain this tendency for the development of this type of dementia. On the other hand, Portugal is the European country with the highest consumption of fatty fish, which seems to be associated with a lower risk of Alzheimer's dementia and there is a lower prevalence among the Portuguese population of the APOE ϵ 4 allele, the most common genetic risk factor for Alzheimer's disease (Ruano *et al.*, 2019). Additionally, it is known that vascular dementia can be prevented by lifestyle modification, so primary prevention measures such as healthy diet, regular exercise and control of major cardiovascular risk factors (Pannain *et al.*, 2019). In previous studies it also has been shown that Physical activity may protect against dementia risk through several mechanisms that facilitates learning, increasing the expression of genes promoting neurogenesis and neural plasticity (Podewils *et al.*, 2005).

Other epidemiological studies by the nature of their community sampling have been able to study risk for AD in racially representative populations. In such studies, older African-Americans have been reported as being more likely than older Caucasians to develop AD and other dementias two or three times higher (Gurland *et al.*, 1999; Dilworth-Anderson *et al.*, 2008; Potter *et al.*, 2009; Barnes and Bennett, 2014; Alzheimer's Association, 2015). These data are complemented with others from a recent study (Chen & Zissimopoulos, 2018) who showed the importance of quantifying the interethnic differences of dementia and of understanding its mechanisms to contribute for the development and implementation of interventions, therapeutics, and to tackle public policies for reducing and eliminating racial and ethnic differences in dementia.

By 2050, according to The Alzheimer's Association annual report (2010), the proportion of racial minorities with AD will increase from 20 to 42%, with African-Americans increasing from 9 to 12%. A more recent report suggests that 16% of African-Americans were diagnosed with AD or other dementias compared to 8% of Caucasians (Alzheimer's

Association, 2015). In another study of Tuerk & Sauer (2015), African-Caribbean patients were diagnosed with dementia on average 4.5 years younger than their White British counterparts and were more likely to be diagnosed with a vascular or mixed type dementia. The scores on initial cognitive testing were significantly lower in the African-Caribbean group, possibly representing more advanced disease at presentation. In 2010, according to the United Kingdom national development strategy for dementia (Banerjee, 2010), the number and proportion of afrodescendent and minority ethnic people with dementia was set to increase sharply over the next years. A survey of clinical dementia centers across Europe found varying levels of access by this specific group of patients and that where these patients did access services, diagnostic evaluation was more challenging owing to language barriers and the availability only of cognitive assessment tools validated in Western cultures (Nielsen *et al.*, 2011). Older Chinese and Vietnamese patients in Australia were believed to present to memory services at a more advanced stage of cognitive impairment because linguistic and cultural complexities may have contributed to longer waits for diagnosis in primary care (Lee *et al.*, 2011). Afrodescendent and minority ethnic people with dementia populations were diagnosed with dementia at an earlier age in one Danish study (Nielsen *et al.*, 2011) and similar barriers to help-seeking for caregivers of patients with dementia were evident in research from both Australia and the USA. These studies emphasize the importance of the international recognition of the growing need for culturally sensitive memory services in USA, Australia and Europe (Haralambous *et al.*, 2014). Also, several studies have been linked the decrease of dementia risk with the improvement of cardiovascular health and the rise of educational levels (Chen & Zissimopoulos, 2018) suggesting that racial and ethnic disparities in dementia prevalence might change over time depending on both changes in risk factors and variation in their relative impact for the various ethnic groups.

1.1.4 Diagnostic and Clinical characteristics

The diagnostic criteria for dementia incorporate the scientific knowledge and technological advances gained in recent times and reflects the contemporary state of understanding regarding the detection and diagnosis of dementia and related disorders characterized by cognitive impairment. Dementia, especially AD, has emerged as one of the biggest threats to public health and personal wellbeing among older adults. In 2011, the National Institute on Aging and the Alzheimer's Association published new diagnostic guidelines for this disease to improve current diagnosis and establish research priorities for the future.

Also in 2013, the American Psychiatric Association published the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) that is similar to the DSM-IV-R but due to this new clinical criteria value Dementia was renamed 'major neurocognitive disorder' and also recognizes earlier stages of cognitive decline as 'mild neurocognitive disorder'. Another clinical reference diagnostic guideline is the International Classification of Diseases published ICD-11 by the World Health Organization in June 2018. ICD-11 adopted the terminology 'neurodevelopmental disorders' and very similar diagnostic criteria to those of the DSM. The aims of all this reclassification is for reducing stigma associated with dementia and bringing the diagnostic guidelines into line with current clinical practice. However, the term dementia may still be used as an acceptable alternative.

Therefore, the general diagnostic criteria for dementia is characterized by 'major neurocognitive' (NCD) acquired deficits, which represent a decline from previous functioning, rather than neurodevelopmental deficits present from birth or early life. There are 6 (six) cognitive domains which may be affected in both MCI and Dementia: (1) *Complex attention* and information processing speed; (2) *Executive function*, decision making, mental flexibility and working memory; (3) *Memory and Learning*; (4) *Language*; (5) *Perceptual-motor function* and (6) *Social cognition*, which includes recognition of emotions, theory of mind and insight. The specific criteria for differential diagnosis of subtypes of dementia is based on examination of potential etiology causes. In many cases there is evidence of a causative disorder, such as Stroke and TBI; Huntington's disease or HIV infection. In others, the cognitive symptoms emerge first and progression provides evidence of a causative disorder such as AD or Lewy body disease. In many cases, especially for older people, there are multiple causative factors, and the diagnosis should recognize this. And there is an increasing understanding that other cognitive domains not only memory, such as language or attention, may be impaired first, or exclusively, depending on which parts of the brain are affected by the underlying disease.

1.1.5 Clinical Assessment

Clinical evaluation in the diagnosis of dementia may be performed in a memory consultation with a neurologist and a neuropsychologist with objective observation; record of clinical and family history with the main complaints and time of evolution of the first symptoms. Additionally, more specific neurological and neuropsychological examinations may be

requested, such as neuropsychological assessment neuroimaging or neurophysiological examinations; blood tests or genetic tests. In general, portuguese public hospitals are not routinely requiring autonomic examination of dementia patients unless there are clinical suspicions of a serious autonomic failure. In addition, the number of professionals with the appropriate competences to perform a credible autonomic evaluation is very small.

Regarding quantitative neurocognitive assessment based on psychometrics, there is the neuropsychological assessment that uses quantitative and qualitative techniques in the form of standardized batteries (Beaumont, 2008; Kolb & Whishaw, 2003). The cognitive deficit diagnosis is based on the comparison between the results of the subject and those of normative subjects (D'Amato & Hartlage, 2008). This type of higher nervous functions examination is a noninvasive functional examination that measures brain activation of diverse neurocognitive and neurobehavioral domains based on performance in qualifiable psychometric tests with a qualitative assessment of the functional autonomy level of the patients and their quality of life.

According to the Portuguese Psychology Association (2019) based on the American Psychology Association definitions, neuropsychology is a scientific area that researches the multiple relations between cognitive and mental functioning, its neurobiological correlates and the behavior of the individual in different contexts and phases of the life cycle. Neuropsychology uses a variety of methods and techniques from Psychology and Neuroscience, being a specialty of clinical and health psychology implemented in the Portuguese national health service at central acute hospitals and in primary health care units.

The development of methods and techniques in neuropsychology for assessment, diagnosis and intervention was widely stimulated during the period that comprised the two great wars (1914-1945) for the need to create neuropsychological rehabilitation programs for military victims of brain injury such as stroke and TBI (Kolb & Whishaw 2003; Lezak 2004). The 20th and 21st centuries have contributed to the clinical neuropsychology field through the development of functional neuroimaging, the integrated brain and mind research and by urging the implementation of public health policies on aging and mental-health care (Kolb & Whisahaw, 2003).

There are tests and scales for neuropsychological evaluation specifically translated and validated for the Portuguese population as recommended since 2011, by DGS. These measurement instruments take into account socio-demographic factors such as age;

education and culture. The most common and reliable neuropsychological screening tests used in Portuguese clinical practice include the *Mini Mental-State Examination* (MMSE Folstein, Folstein, & McHugh, 1975), the Washington University Clinical Dementia Rating Scale (CDR; Morris, 1993) and the *Subject Memory Complaints questionnaire* (QSM; Schmand *et al.* 1996; Ginó *et al.*, 2007) which application to designed patients are useful both to clinical diagnosis, to clinical trials and dementia research.

In the field of cognitive trait tests, MMSE has a scale score ranging from 0 to 30 with higher scores indicating a better cognition. This scale has six subdomains each of them as a certain sub-score rating, which includes *orientation* (10 points maximum), *retention* (3 points maximum), *attention and calculation* (5 points maximum), *deferred evocation/recall retention* (3 points maximum), *language* (8 points maximum) and *visual-constructive ability* (1 point maximum). The norms in this instrument have been successively improved by considering variables such as age and schooling, both influencing MMSE scores, as well as, the definition of cut-off points (Guerreiro *et al.*, 1994; Morgado *et al.*, 2009; Freitas, Alves & Santana, 2012). MMSE is a valid tool for frequent diagnosis of mild cognitive impairment or other forms of dementia, used in consultations specializing in different levels of health care, and is more sensitive to AD screening (Santana *et al.*, 2016) but it should be emphasized that a high MMSE score does not exclude the possibility of dementia.

CDR is a global assessment instrument that yields global boxes scores used in clinical and research settings for staging dementia severity. Is a 5-point scale used to characterize six domains of cognitive and functional performance - Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies and Personal Care- applicable to Alzheimer disease and related dementias. The needed information to achieve each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g. family member) referred to as the CDR Assessment Protocol with previous revision criteria (Tractenberg *et al.*, 2011). The CDR scoring provides descriptive anchors which guide the clinician in making appropriate ratings based on interview data and clinical judgment. In addition to ratings for each domain, an overall global CDR score may be calculated through the use of an appropriate algorithm. CDR scores are useful for characterizing and tracking patient's level of impairment/dementia: 0 = *Normal*; 0.5 = *Very Mild Dementia*; 1 = *Mild Dementia*; 2 = *Moderate Dementia* and 3 = *Severe Dementia*. CDR global score has several advantages for detection of dementia among healthy elderly, being a reliable diagnostic standard measure (Chaves *et al.*, 2007) and can accurately diagnosis MCI or AD in most patients having global CDR scores of 0.5 (O'Bryant *et al.*, 2008).

The subjective memory complaints are an important clinical factor and a frequent problem in primary health care in adult and older people (Eichler et al., 2015). The relationship between subjective perception of memory and performance in objective tests has been widely investigated given its clinical relevance in the diagnosis of cognitive impairment with significant partial correlations found in tasks related to working memory, verbal episodic memory, and long-term semantic memory providing additional evidence of the clinical relevance of the subjective perception of memory evaluation (Bourscheid; Mothes & Irigaray, 2016). For that reason, QSM is a clinical tool that investigates subjective memory complaints that represent a type of concern made by people with cognitive difficulties, very common in elderly individuals (Young et al. 2000). For example, in community-based studies, their reported prevalence was 25%-50%, and more than half of elderly individuals with subjective memory complaints were worried about incipient dementia, specifically, AD (Mitchell et al. 2008). This questionnaire has ten questions, and the scoring of each item on the scale ranges from 0 (zero), 1 (one), 2 (two) or 3 (three) points depending on the type and severity of the complaint, can reach a maximum of 21 points. For the Portuguese population values greater than or equal to 4 points are indicative of the presence of significant memory complaints. In a longitudinal study carried out in a primary health care of the Central Region of Portugal, to characterize the QSM according to socio-demographic, clinical, cognitive, emotional and quality of life variables, was demonstrated that subjective memory complaints might be an important symptom for the early identification of individuals at higher risk for developing a dementing process (Sousa *et al.*, 2017).

1.1.6 Prognosis and its relation to ageing

The causes of aging can be related to some damage concept theories whereby the accumulation of damage such as DNA oxidation may cause biological systems to fail (Burrows & Muller, 1998) or to the programmed aging concept, whereby internal processes such as DNA methylation may cause ageing (Evans & Evans, 1970).

In humans, ageing represents the process of becoming older and, therefore, the accumulation of changes along time encompasses physical, psychological and social modifications. Ageing is a condition of functional vulnerability that can lead to disease resulting from structural or functional disturbances due to internal or external causes, as the body and the brain grow older (Hayflick, 2000). Aging is the greatest known risk factors for most human diseases. Therefore, age has been also identified as the strongest risk factor for AD, the most prevalent

form of dementia as it is predominantly a disorder of later life.

Beyond *old age*, ageing and dementia are also associated strongly with some demographic, co-morbidities and lifestyle risk factors related to the onset symptoms of the neurodegenerative pathologies, such as: being a woman, low education and low social class; diabetes, vascular disease, stroke, hypertension, depression, smoking and reduced physical activity (Wu *et al.* 2016). But, there are numerous biopathological and cognitive-behavioral changes which are associated with normal ageing, being many of these the same as the changes attributed to dementia. For this reason, we can assume that physiological changes due to dementia can be confounded with age-related changes. On the other hand, it seems consensual that normal ageing and dementia are a continuum, the changes differing in degree but not in kind (Huppert, Brayne & O'Connor, 1994).

At a neurocognitive level there is a decline in various functions such as the manipulation of information in working-memory, retrieval of names, reaction time, declarative memory and information processing. And, these cognitive impairments – also the normal deterioration observed in ageing - can be misled with the symptoms of dementia, and there is great debate over whether dementia is simply an extension of old age or a disorder that is separate from it.

Therefore, ageing mechanisms may be more pronounced in patients with dementia due to the occurrence of dysfunctions in cerebral structures that coordinate visceral functions such as the cardiovascular, digestive and respiratory ones which are also part of the central autonomic network. At cardiovascular level, new specific studies (Lane *et al.*, 2019) using also neuropsychology assessment with cognition performing tasks and positron-emission tomography-MRI scanner, suggest that continuous high blood pressure and sudden increases in BP are associated with brain pathologies in later life like the increase of white matter hyperintensity and smaller brain volumes. Having high blood pressure would also increase the risk to dementia during life and this is a risk factor for this neurodegenerative pathology.

1.1.7 Therapeutic approaches

The dementia treatments attempt on alleviating the impairment of memory. The neuropharmacological treatment may lead to some improvement in cognitive memory performance (Cameron *et al.*, 2000; Evans *et al.*, 2003) and functional abilities with more participation in daily activities and therefore a reduce of total costs and time spent by

patient and caregivers (Reisberg *et al.*, 2003). The cholinergic hypothesis of AD led to drug development that specifically sought to redress the loss of cholinergic neurons and neurotransmitters. The mechanism of action for these drugs is the inhibition of the enzyme acetylcholinesterase (Winblad *et al.*, 2016) and the role of the cholinergic system in memory was encouraged by studies in which scopolamine, a cholinergic antagonist, produced amnesia in healthy individuals. Scopolamine was normally administered with analgesia during surgery; women in labor would report not being able to recall events during the delivery when they were given scopolamine (Thal, 1992).

Based on effects of scopolamine on both neurochemistry and cognition, work began into developing new drugs that would prolong the action of acetylcholine. One of such drugs, physostigmine, appeared to have a significant positive affect on verbal and non-verbal memory when given intravenously (Christie *et al.*, 1981). Another one, tetrahydroaminoacridine, also appears to produce improvements in verbal memory (Kaye *et al.*, 1982). However, the response to these and other drugs can be variable due to a number of psychopharmacological factors, among them the fact that some agents are poorly absorbed, do not cross the blood-brain barrier and have severe side-effects. Currently, the specific and potent clinical acetylcholinesterase inhibitors most commonly used are *donepezil*, *rivastigmine* and *galantamine*, for the treatment of mild and moderate dementia. *Memantine*, a non-competitive agonist of N-methyl-D-aspartate receptors has been used in the treatment of moderate to severe Alzheimer disease. Other drugs under review are the anti-inflammatory ones, because the incidence of AD is low in sufferers of rheumatoid arthritis who are taken them and antioxidants such as vitamin-E. However, none of them has been shown to demonstrate consistent therapeutic efficacy (Bullock, 2002). Another putative treatment currently under investigation involves the removal of the amyloid protein.

Also non-pharmacological measures introduced in the prevention and rehabilitation of dementia has been shown to be effective when combined with drug administration. These include the psychological and psychotherapeutic support, the psychoeducation and the cognitive intervention adjusted to a healthy and neuroprotective lifestyle. There is consistent evidence from multiple clinical trials that programmes of cognitive stimulation consistently benefit cognition in people with mild to moderate dementia over and above any medication effects (Woods *et al.*, 2012). Cognitive stimulation is also associated with increase of patients quality of life, well-being and communication in addition to any medication effects (Aguirre *et al.*, 2013). However, other outcomes need more exploration to reinforce the potential benefits of longer-term cognitive stimulation programmes and to

strengthen their clinical significance.

1.1.8 Impact of dementia on Quality of Life

Dementia is receiving increasing attention from governments and politicians. Epidemiological research based on western European populations done 20 years ago provided key initial evidence for the dementia policy making, but these estimates are now out of date because of changes in life expectancy, living conditions and health profiles (Wu *et al.*, 2016). Although life expectancy at birth continues to show substantial variation between social environments across countries, previous research shows that combined prevalence estimates in western Europe are reasonably consistent across countries (Hofman *et al.*, 1991). But the trends in prevalence and incidence of dementia are likely to be modulated by a complex combination of societal changes affecting survival, lifestyle factors, cultural, genetic and health profiles across life stages.

In Portugal, the economic, social and psychological costs for the families of patients with dementia are very high. Together with the ability of the institutionalization of patients in nursing homes, some specialized rehabilitation dementia units of the Portuguese national health system, applying neurocognitive-behavioural rehabilitation and socio-occupational reintegration programs whenever possible, are starting to be developed to support these patients and their families. There is also the Portugal Alzheimer Association a private institution social solidarity founded in 1988 by Professor Carlos Garcia (1936- 2004), a nationwide organization, that highly promotes the quality of life of people with dementia.

Although public awareness about dementia is increasing it is still limited, being necessary to improve the literacy about it as well as social education. In fact, there is still a great lack of knowledge regarding the signs and early symptoms of dementia and the responses for the diagnose and intervention process in the community are very limited. False beliefs, stigmas and unconstructive attitudes associated with dementia still persist and adversely affect the patients and their caregivers' quality of life (Wu *et al.*, 2016). Several studies have shown differences on morbidity among elderly patients with dementia of different ethnicities and cultures, on the prevalence of behavioral and neuropsychiatric symptoms, on how education and the belief system influence the cognitive changes experienced by the patients themselves and on the time-point when patients seek help from the health services for diagnosis and treatment (Wykle *et al.*, 1991; Sink *et al.*, 2004; Gillum *et al.*, 2011; Mukadam *et al.*, 2011).

In Portugal, until the present, we are not aware of any study in ethnic communities regarding patients quality of life despite some differences between white and afrodescendent caregivers in the cope strategies with distress have been reported in others international studies (Kneebone *et al.*, 2003; Broday *et al.*, 2009 and Pinquart *et al.*, 2005). The relationship between ethnicity, race and dementia in epidemiological perspective can be influenced by cultural factors more or less protective related to symptom management, as they may influence the way how patients and their family's value and recognize the progression of the disease. On the other hand, ethnic or racial differences are often associated with immigration phenomena, education level, beliefs and socioeconomic status. Patients with dementia and their caregivers may also use different languages, religious beliefs or cultural practices distinct from those in health services, which may constitute itself a social minority group segregation and a barrier to access the appropriate treatment (Lliffe *et al.*, 2004).

Lifestyle factors, identified as diet, physical activity and sleep hygiene, play an important role in the development, progression and treatment of dementia as they are closely link to dementia risk factors. A recent report from Alzheimer Association refers that around 1/3 of the dementia cases can be prevented by introducing lifestyle measures in the patient daily life which are inexpensive comparing with the pharmacological therapeutics (Lancet, Alzheimer research UK). In fact, not smoking, doing exercise, keeping a healthy weight, treating high blood pressure and diabetes together with nutritional counselling can all reduce the risk of dementia (Alzheimer Research UK). Despite needing more evidence, additional measures of social and cognitive stimulation, mood changes evaluation and improved self-management may also help cognitive function improving this patient's quality of life (Alzheimer Research UK).

In a way to find new clinical approaches and a close relation between the clinical teams, the patients and their families/caregivers, personal health systems for the management of progressive diseases have been developed under the recent years both as research prototypes (e.g. EU funded MyHeart, Heart Cycle, Metabo projects) and commercial products (e.g. Philips Motiva or IntelGE Care Innovations guide). These solutions offer vital signs monitoring and therapy delivery at home but focusing on physical conditions rather on providing support for cognitive or psychological treatment which is still lacking.

1.1.9 Health economics related to dementia

The national and global economic and social impacts due to the prevalence of dementia in

ageing have been an incentive for the pursuit of innovative treatments based on clinical research especially on multicenter clinical trial methodology. For instance, the current cost of caring patients with dementia Alzheimer's treatment in the UK alone is estimated to be between 6 billion € and 16 billion € per year (McNamee et al., 2001; Lowin et al., 2001), but no current treatment is able to halt the progress of AD. A recent USA study, the CARE study (= *Costs, Accountabilities, Realities and Expectations*) promoted by the Northwest Mutual Insurance indicated that caregivers in the USA are spending more money on caring than it was financially planned. This study found that 7 in 10 caregivers reported lowering their own spending to be able to pay for caregiving costs for a parent or senior loved-one. Data from the study were gathered from online surveys among 1,004 adults, aged ≥ 18 . The demographics of the people polled included over 200 persons aged 35-49 and just over 700 experienced caregivers. The report was published in March of 2018. About the cost of Dementia Care report include the following facts and figures:

1. 67% of caregivers reported reducing their own living expenses to pay for caregiving costs (this number was up from 51% last year);
2. 57% of future caregivers expect to have personal costs of providing care, but 48% have not planned financially (a jump from only 35% last year);
3. 53% of American caregivers say the caregiving situation was not planned and many were financially unprepared for the event;
4. Only 48% of caregivers reported that they were financially ready to provide financial support;
5. 34% of current caregivers report their monthly spending on caregiving-related expenses is between 21-100% of their budget.

Another report from the Alzheimer's Association further tackles this point by detailing the cost of dementia care in the USA and its impact on families:

- In 2017, 18.4 billion hours of care, valued at \$232 billion, were provided by the family and unpaid caregivers;
- 83% of the help provided to older adults in the USA come from family members, friends and other unpaid caregivers;
- The total lifetime cost of care for someone with dementia is estimated to be \$341,840, with the costs associated with family care to be 70% of lifetime dementia care costs;
- 41% of dementia caregivers have a household income of \$50,000 or less.

In 2013, the authors of the World Alzheimer Report estimated that 44 million people were having dementia worldwide, causing a substantial economic cost for the overall society. In 2017, was estimated that the total economic costs due to dementia increased from US\$279 billion in 2000 to \$948 billion in 2016, with an annual growth rate of 15%. This included costs of informal care at \$95 billion in 2000 and \$401 billion in 2016, with the annual growth rate of 21%. Regional differences in the economic burden of dementia exist, and the highest economic burden was found in Europe and North America (Xu *et al.* 2017). For that, dementia is a substantial economic burden worldwide and a global and regional strategic action plan for dementia will be important to be followed to reduce the future burden of dementia.

In Portugal, the estimated number of people with dementia among those aged ≥ 60 years, is 160.287, representing 5.91% of this population-stratum. Knowing Alzheimer's disease is responsible for 50-70% of all cases, we might conclude there are between 80144 and 112201 patients. According to a recent population-based study, 76250 receive anti-dementia drugs and the costs of this kind of medication is 37 M€/year (Santana *et al.* 2015). And apparently, not all Alzheimer's disease patients receive the recommended medication, suggesting that this condition is still under-diagnosed. However, figures indicate a positive progression with an increment of treated cases and a reduction of medication-costs (Santana *et al.*, 2015).

1.2. Pathophysiology of Dementia: major pathophysiological and neuropathological mechanisms

Alzheimer's disease presently is the commonest cause in the developed world, causing a cortical-subcortical degeneration of ascending cholinergic neurons and large pyramidal cells in the cerebral cortex. Clinically, the disease reflects predominantly deterioration of function in the association cortex. Pharmacologically and pathologically, abnormalities are more diffuse and extend into sensorimotor cortical areas as well.

Post mortem, the brains of AD patients show shrinkage primarily of the frontal and temporal gyri (up to 20%) and ventricle enlargement. There is the possibility that the shrinkage is due to normal ageing, because not all AD patients exhibit shrinkage. There is neural loss in the cortex, hippocampus, amygdala, basal forebrain, locus coeruleus, raphe nuclei and

nucleus basalis of Meynert. The classic pathological symptoms of AD are (1) neurofibrillary tangles, (2) senile plaques, (3) granulovacuolar degeneration and (4) Hirano bodies. There are abnormal amyloid protein deposits in the demented individual's brain (Muller-Hill and Beyreuther, 1989). Neurofibrillary tangles are straight or paired helical filaments that collect intracellular and are made up of special proteins (tau-protein). Tangles normally consist of a pair of helical filaments found in the cytoplasm of cortical and hippocampal pyramidal cells (Gallo and Anderton, 1989) and the amyloid β -protein is responsible for the formation of the senile plaques (Anderton, 1987). Temporal, parietal and frontal areas are specially affected by tangles. The tangles do not appear with normal ageing, although they are found in other dementias. Senile plaques are spherical and are made up of glia and abnormal nerve cell processes; these surround the extracellular amyloid proteins (usually β -amyloid). Senile plaques in the cortex are more pronounced in AD patients than in age-matched controls and some patients exhibit tangles but not plaques. Granulovascular degeneration occurs primarily in the hippocampus and, as the name suggests, results in neuronal tissue becoming full of holes. Finally, Hirano bodies are rod-shaped material that intrudes on neurons. The lesions neuropathological features appear most commonly in the hippocampus and entorhinal cortex in the early stages of the disease, later extending to the frontal, temporal and parietal lobes. Hippocampal and entorhinal abnormalities have been found to correlate with the severity of episodic memory impairment in the disease (Rémy *et al.*, 2005).

There is evidence of metabolism reduction in frontal, parietal and temporal regions and areas of metabolic reduction tend to be positively correlated with neuronal degeneration (Haxby *et al.*, 1994).

A loss of synapses in the AD brain has also been observed in certain pathways, which appears to correlate with the loss in intellectual function, these including cortical acetylcholine, acetylcholinesterase and nicotinic receptors (Terry *et al.*, 1991).

In the mid-1970s, it was found that a loss of up to 70% of choline acetyltransferase, the cholinergic marker enzyme that synthesizes acetylcholine, occurs in the temporal and parietal cortices of these patients. This acetylcholine synthesis impairment is correlated with the severity of the dementia, and the loss of choline acetyltransferase is correlated with the number of senile plaques and the degree of dementia (Perry *et al.*, 1999). In addition to the cholinergic system other neurotransmitter system has been implicated in AD, for example, serotonin and noradrenaline neurons markers have been found to be reduced in the cortex (Mann *et al.*, 1982), a reduction possibility due to the loss of projections from the dorsal raphe and locus coeruleus to the cortex. Reductions in the concentration of

cortical noradrenaline have been found in a large number of other studies especially in the cingulate gyrus (e.g. Gottfries, 1990; Cross *et al.*, 1984).

1.3 Dementia and Autonomic function

Autonomic dysfunction may result from primary modifications of the autonomic nervous system or be secondary to a wide range of diseases that cause severe morbidity and mortality. The autonomic nervous system, as a whole, is organized as a reflex arc being the sympathetic and the parasympathetic systems the motor portion of this reflex arc that also includes integrative centers located in the central nervous system (the central autonomic network) to which sensory information is conveyed from peripheral sensors located in specific reflexogenic areas. Stimulation of different parts of the cerebral cortex and the limbic system, which are relay stations of the central autonomic network, also produces autonomic effects and the higher centers of the brain can abnormally influence the activities of the autonomic nervous system and induce disease such as cardiac palpitations (arrhythmias) and even myocardial infarction. The evaluation of the autonomic performance and influence upon peripheral functions is performed through standard autonomic manoeuvres which are conceived to provoke the system and evaluate its dynamicity in terms of presence or absence of response, duration and magnitude.

Usually, due to the nature of the recording devices, most maneuvers target the cardiovascular system and are non-invasive in nature. To avoid stimuli interference on ANS responses, autonomic evaluation should be performed in a dedicated laboratory with control of temperature, humidity, noise and environmental light by experienced technicians and under medical supervision.

Patients undergoing autonomic evaluation should not consume food or tobacco, at least four hours before testing, and alcohol, at least 12 hours, before the evaluation, which should be performed during the morning. Medications, particularly those that directly affect the autonomic nervous system should be discontinued according to the drugs' half-life and the patient's condition. Due to the high data variability, both intra and inter-individuals, normal values are set by each laboratory and should be grouped by gender, age and decade of life (Low and Benarroch, 2008; Mathias and Bannister, 2012; Laranjo *et al.*, 2017). The evaluation and data analysis protocols should also be appropriate to the study. Heart rate response to deep breathing, blood pressure and heart rate changes upon Valsalva manoeuvre and active standing are classical autonomic tests (Ducla-Soares *et al.*, 2007; Xavier *et al.*, 2008; Low and Benarroch, 2008; Mathias and Bannister, 2012). The gain or sensitivity of the baroreflex (BRS) as well as its efficacy are measures of the baroreceptor

function which is one of the main mechanisms regulating blood pressure in each moment. BRS can be assessed under dynamic or steady-state conditions by various methods correlating blood pressure spontaneous fluctuations with consecutive heart rate changes. The sequential method is one of those methods and searches for blood pressure and RR ramps (Di Rienzo et al, 1983). A ramp is defined as a variation of, at least, 1 mmHg and 4 ms between adjacent values of blood pressure and RR, respectively. This concept can only be applied to three or more cardiac cycles varying monotonically, either increasing or decreasing. When a BP ramp occurs at the same time as an RR ramp, a BRS event is identified. The baroreflex effectiveness index (BEI) is the ratio between the total number of BRS events and total number of pressure ramps, increasing or decreasing, for a given period. BEI is an indicator of the effectiveness of baroreceptor-mediated cardiac regulation (DiRienzo et al, 1983; Laranjo et al, 2017). Signal processing can be applied to autonomic evaluation in the time, frequency and time-scale domains can identify different pathological response profiles, such as delays in adaptive responses to provocative maneuvers, dyssynergia between BP and HR responses, and/or exaggerated responses such as orthostatic hypotension, postural orthostatic tachycardia and syncope.

In particular, fast Fourier transform (FFT) has been widely used (Pagani et al, 1986; Laranjo et al 2017). By decomposing the signals it achieves a range of low (LF; 0.04-0.15 Hz) and high frequencies (HF; 0.15-0.4 Hz) linked to sympathetic and parasympathetic nervous systems (Task Force ESC, 1996) FFT analysis requires a stationary signal and a long period of data collection, of at least 5 min and it cannot locate and follow changes in a frequency over time which are overcome a wavelet-based. Wavelet coherence can also be used to analyze the degree of autonomic remodeling in patients under specific therapeutic schemes.

Prefrontal cortex activity has been associated with changes to heart rate variability (HRV) a measure of autonomic nervous functioning, via mediation of the cortico-subcortical pathways that regulate the parasympathetic and sympathetic branches of the autonomic nervous system (ECS, 1996). Changes in HRV due to altered prefrontal suggests that prefrontal hyperactivity increases parasympathetic tone and decreases contributions from the sympathetic nervous system (Thaye and Sternberg, 2006). Alteration of prefrontal cortex activity has been independently demonstrated to modulate HRV using both non-invasive brain stimulation (Brunoni AR *et al.*, 2013) and cognitive tasks reliant on prefrontal functioning (Laborde *et al.*, 2015). Therefore, activation of the prefrontal cortex results in change to HRV (Lane *et al.*, 2001; Napadow *et al.* 2008) which can be thought of as a measure of the aggregate effect of activity in a complex brain network, regulated top-down by the

prefrontal cortex. According to this model, hyper-activation of the prefrontal cortex inhibits the sympathoexcitatory circuit of the amygdala, which is known to have outputs relevant to autonomic regulation (Thayer and Sternberg, 2006). This in turn reduces sympathetic activity and parasympathetic suppression, culminating in a reduction in heart rate.

In this context it has been found that autonomic failure of patients with neurodegenerative disorders may occur (Borson *et al.*, 1992; Chu *et al.*, 1994; Algotsson *et al.*, 1995; Kaufmann *et al.*, 2003). The autonomic nervous system together with the endocrine and the immune systems contributes to the maintenance of homeostasis by function controlling and its dysfunction may result from primary neurological diseases (Ducla-Soares *et al.*, 1993; Mathias & Polinsky, 1999; Goldstein *et al.*, 2002; Kaufmann & Biaggioni, 2003). In these cases Parkinson's disease, dementia with Lewy bodies, multiple system atrophy and Alzheimer's disease are the most prevalent related neurodegenerative disorders (Kaufmann *et al.*, 2003). However, the most severe dysautonomia are usually related to traumatic or vascular cerebral pathology (e.g. traumatic brain-injury or cerebrovascular infarction) as the targeting of areas of the central autonomic network is more effective.

In a study conducted by Ballard (1998) there was a prevalence of autonomic system changes in 57% of patients with AD (eg.: orthostatic hypotension, vasovagal syncope and carotid sinus hypersensitivity). Other studies were consistent in demonstrating autonomic dysfunction in these patients (Aharon-Peretz *et al.* 1992), such as the exacerbation of the sympathetic system with relative depression of the parasympathetic system (Vitiello *et al.*, 1993), blood pressure response dysfunction to the standing posture test and decreased parasympathetic function at rest and during deep breathing (Wang *et al.*, 1994; Ferini-Strambi *et al.*, 1997). Another study demonstrated a greater decrease in blood pressure during orthostatic position in AD patients compared to controls (Allan *et al.* 2005; 2007). It also observed the sympathetic involvement in alpha-synucleinopathies including dementia with Lewy bodies. In those patients, MIBG uptake was demonstrated to be reduced (Miyamoto *et al.*, 2008) as well as the plasma norepinephrine concentrations in supine and standing positions.

The dysfunction of cortical systems involved in memory processes are the most investigated in AD, however, a possible mechanism for the neurobiological substrates of autonomic deregulation can also be cortical area dysfunction. At this level again, neuroanatomical, lesion and electrophysiological studies evidenced the role of the prefrontal cortex ventromedial and orbitofrontal area and anterior insula (Neafsey, 1990; Cechetto and Saper, 1990), projecting directly to important subcortical autonomic centers (e.g. amygdala,

thalamus, hypothalamus, cerebellum and brainstem). The hyper-excitability in these areas can cause lethal arrhythmias and myocardial infarction (Oppenheimer *et al.*, 1992). These patients, when faced with the need to respond to demanding cognitive challenges (Borson *et al.*, 1992) or emotionally intense stimuli (Chu *et al.* 1994) triggered dysautonomia due to the failure to coordinate between higher mental activity and somatic response which, at the level of autonomic dysfunction, represents an important pathogenesis (Aharon-Peretz *et al.*, 1992; Algotsson *et al.*, 1995).

These observations have led to the understanding that healthy physiologic function is a result of continuous, dynamic interactions between multiple neural, hormonal, and mechanical control systems at both local and central levels. The interactions between autonomic neural activity, BP, and respiratory control systems produce short-term rhythms in HRV measurements (Hirsch and Bishop 1981, 1996; McCraty *et al.*, 2009). The most common form for observing these changes is the heart rate tachogram, a plot of a sequence of time intervals between R waves. Efferent sympathetic and parasympathetic activity is integrated in and with the activity occurring in the heart's intrinsic nervous system, including the afferent signals occurring from the mechanosensitive and chemosensory neurons, all of which contribute to beat-to-beat changes. HRV is thus considered a measure of neurocardiac function that reflects heart-brain interactions and ANS dynamics (Mateo *et al.*, 2011). HRV can also be an indicator of psychological resiliency and behavioral flexibility, reflecting the individual's capacity to adapt effectively to changing social or environmental demands (Beauchaine, 2001; Berntson *et al.*, 2008). Several studies have shown an association between higher levels of resting HRV and performance on cognitive performance tasks requiring the use of executive functions (Thayer *et al.*, 2009) can be increased in order to produce improvements in cognitive function as well as a wide range of clinical outcomes, including reduced health care costs (Lehrer *et al.*, 2003; 2008; McCraty *et al.*, 2003; Bedell and Kaszkin-Bettag, 2010; Alabdulgader, 2012).

Dementia seems to develop differently in the brain of afrodescendent patients than in whites. Afrodescendent people apparently are more likely to suffer different types of brain changes as microstrokes, Lewy bodies development and blood vessel disease, that will also contribute to dementia (Barnes *et al.*, 2015). These findings suggest that afrodescendent patients might have different risk factors for dementia which may be related to specific genetic differences and to the high prevalence, in this population, of heart disease, high blood pressure and type 2 diabetes (Barnes *et al.*, 2015). The later are a group of risk factors for brain strokes and run with autonomic dysfunction since the earlier stages. Thus, learning the differences between afrodescendent and white dementia patients and their causes will

be critically important to find more specific therapeutics for dementia which could also address the expression of the disease among ethnicities and improve the support to these patients, their families and caregivers.

1.4. The Recruitment of vulnerable populations into research

Although it is implied that minorities are adequately represented in clinical trials and other investigational studies, they still have low inclusion rates in health research compared to non-minority groups. Certain social groups continue to be excluded from social research, being as an example, women, sexual minorities and ethnic minorities, among others (Cundiff, 2012). In the last decade some authors have been dedicated to review the situation of these minority populations (UyBico, Pavel & Cross, 2007), having identified several specific barriers to the recruitment of minorities for research studies which can be grouped essentially into three types: institutional, from the researcher and from the patient. The former is mainly related to administrative and time constraints regarding the research sponsor while at the researcher level are included multicultural differences, lack of knowledge of the research project and methods and non-acceptance of the project leadership.

Barriers at the patient level include distrust of research, lack of confidentiality, insecurity, poor access to medical care, lack of knowledge, language comprehension and cultural differences (UyBico, Pavel & Cross, 2007). The researcher access to this social excluded groups can fail because some classical sampling methods are ineffective or inappropriate regarding group's social or physical location, vulnerability, or otherwise hidden nature (Ellard-Gray, *et al.* 2015). When a population is difficult to access, researchers generally describe them as *hard to reach populations* because of their physical or social locations (e.g., remote geographical location, social elites or social culture issue), but they may also be hard to reach because they are vulnerable (i.e., disenfranchised, subject to discrimination or stigma) or hidden (i.e., populations with no defined limits or sampling parameters) (Shaghaghi, Bhopal & Sheik, 2011; Sydor 2013).

Despite these barriers, minorities appear to be willing to participate in research studies if given opportunities to do so. One of the possible recommendations regarding this problem is starting from early stages of study design to dissemination of study results. In fact, as the possibility of minority recruitment has increased, research promoters' interest in planning minority recruitment interventions has increased. Suggested approaches include recruiting

through partnerships with churches and community organizations, recruiting at community clinic settings and providing logistical assistance or financial encouragement as well as awareness-raising campaigns that promote disease awareness and behaviour change because recruitment is one of the most significant challenges in conducting research with ethnic minority populations, establishing relationships with organizations that serve ethnic minority communities can facilitate recruitment (Alvarez *et al.*, 2006)

For instance, in Portugal, the Alzheimer Portugal Association; Alzheimer Acores Association and Alzheimer Pinhal Litoral Association are three non-profit organizations dedicated to support people with Alzheimer disease and/or any other forms of dementia and also seek to study and increase the existent knowledge about the disease. These working organizations have been promoted health communication and media strategic communication as the driving forces to promote health literacy matching the carers' needs (Nunes, 2017). In the face of dementia, diagnosed or not, the lack of information may be the reason for resorting to a health service, as an express or indirectly need of the family. Many family members know that dementia causes cognitive limitations, but they do not understand executive deficits, the meaning of apraxia, or delusional symptomatology. Others are blamed for the outbreak (e.g., after a change of address, which may have coincided with the onset of symptoms, at most, by the nonspecific role of stress in the diminished brain reserve). These situations often produce distress and inadequate responses in family members, triggering destructive interactions with the sick person (Gonçalves-Pereira & Sampaio, 2011).

For these psychosocial and cultural reasons, in Portugal, it seems to remain difficult certain groups of patients access to the adequate and timely health care services or, consequently, to the possibility of informed and motivated participation in clinical and scientific research studies, such as controlled clinical trials or other prospective experimental human-models.

However, in the last year 2018, a strategic dementia health plan was approved and published by the Portuguese Ministry of Health (*published in Diário da República n.º 116/2018, Series II of 2018-06-19 by order n.º 5988/2018*). This national plan guiding document may help to contribute in the future to the recruitment of vulnerable populations dementia patients of a specific ethnicity or race, because defines in Portugal “*the principles to be followed by the care of people with dementia, the criteria to be used for preventive intervention, the measures to be taken with regard to early detection, the measures for access to medical diagnosis and comprehensive diagnosis, and the therapeutic responses at the three levels of health care, clarifying a care path for people with dementia, based on the principles of ethics, proximity, accessibility, equity and continuity*”. This strategic plan focuses on issues such as

global economic impact; the stigma; promotion of diagnosis; early intervention; the needs of families and informal caregivers and long-term care, based on best practices developed in reference countries and the World Health Organization (WHO) guidelines; OECD and Alzheimer's Disease International. On this document, greater emphasis has been placed on greater sharing of responsibilities between public, social and solidarity, private and academic institutions and greater public awareness, particularly of decision-makers, of the problem of dementia. Although awareness has been steadily increasing, it remains low in the face of the scale of the problem and there is still a high lack of knowledge about the theme, regarding the signs and symptoms of dementia, the diagnostic and intervention process, or the existing responses in the community. Because false beliefs and unconstructive attitudes associated with dementia persist, negatively affecting the quality of life of people in their teeth and families. Improving awareness and education, developing possibilities for early diagnosis and treatment are among the priority areas identified in the generality of this plan. It is recognized that stigma associated with dementia and a better understanding of this issue can help to reduce discrimination and social exclusion by promoting timely access to diagnosis and health care.

And finally, it is encouraged the creation of innovative technological and research projects with value to the different stakeholders, looking for integrated solutions for the definition of policies and services, and improving the well-being of these patients and their supportive networks (family, caregivers), neighborhood, service providers, etc.).

2. AIM OF THE PRESENT WORK

Central autonomic network stations such as the hypothalamus, the amygdala, the insula and locus coeruleus are affected in the early stages of dementia. Body systems dysfunction such as cardiac, urinary or thermoregulatory have been already reported in dementia investigations but studies on the integrity of the overall autonomic function in dementia has been limited and needed detailed exploration, in particular in cohorts of ethnic patients. Therefore, the overall purpose of the present Master Thesis is to investigate autonomic function in afrodescendent patients with mild dementia.

3. METHODS

3.1. Ethics Statement

The study complied with the Declaration of Helsinki and was submitted to Faculty of Medicine/CAML Ethical Committee, ratified by Fernando Fonseca Hospital Ethical Committee and performed under informed consent.

3.2. Increasing project awareness to facilitate patient's recruitment

Following the approval of this project by the Ethics and Clinical Research Committees of the Lisbon Medical School of the University of Lisbon and the Fernando Fonseca Hospital (HFF), this work was presented to the coordinators of the clinical and health institutions under HFF's geography influence area, to disclose it and to raise resources for identifying participants based on inclusion and exclusion criteria's. For that purpose communication materials have been developed and oral presentations of the project have been done at CERCITOP, CRL and to Clinical and Scientific Commission of Sintra and Amadora ACeS who disseminated the project and its purpose among the various primary care centers of both municipalities. The study was also submitted to the ARS-LVT Ethics and Scientific Committee. This referral network took about a year to be established between 2016 and 2017, based on our belief on the health gains that this academic research work could bring to the clinical practice and to treatment of a vulnerable minority of dementia patients, users of the national health service in the above municipalities.

3.3 Study Population

Non-Caucasian afrodescendent subjects, of both sexes (n=22), aged ≥ 50 years, diagnosed with mild dementia defined in accordance to DSM criteria were enrolled. A group of Caucasian subjects with the same diagnostic criteria of mild dementia (n=7) and a control group of multi-ethnic subjects without cognitive impairment (n=12) matching age and sex were also included in the study.

The participants were recruited and evaluated between February 2018 and May 2019 at the HFF's Neurology Department in collaboration with CERCITOP, CRL upon their first medical appointment due to complaints of cognitive decline. All patients were subjected to history taking, physical examination and an anamnesis of dementia. Drug history, hypertension, dyslipidemia, educational years, occupation and birthplace also recorded. Participants with atrial fibrillation ablation or implantation of a pacemaker, diabetes, chronic obstructive pulmonary disease, orthostatic hypotension, reflex syncope, cardiac arrhythmias, heart failure, those who had undergone cardiac surgery, those who were taken beta-blockers or several psychotropic medications such as tricyclic antidepressants, selective serotonin-epinephrine reuptake inhibitors, atypical antidepressants, antipsychotics and cholinesterase inhibitors or have other significant medical causes of dementia (hypothyroidism, chronic sub-dural hematoma, asthma, multiple sclerosis) were excluded from this study. Due to the age of the studied population some medications were allowed and they included diuretics, peripheral acting calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, serotonin reuptake inhibitors and benzodiazepines.

After the first medical appointment, the identification of possible patients to be included was made but only after confirmation of mild dementia diagnosis based on neurological evaluation and neuropsychological assessment through cognitive and functional tests. If the patient met the study inclusion criteria, then, after a study detailed explanation, which included its purposes and the protocols to be performed, the patient was left free to decide to participate or not in it. If a positive decision was made, then an informed consent document was signed and the patient enrolled (Figure 1). Of the initial group of identified patients only a small number of them was included fulfilling all the study requirements.

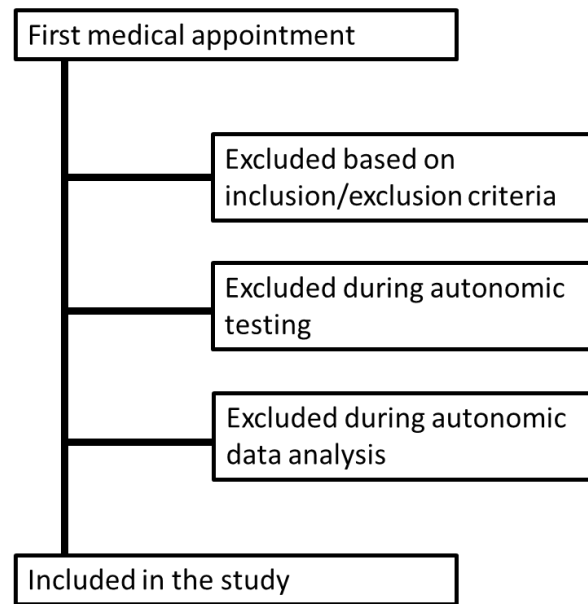


Figure 1. Flow chart of the study inclusion steps.

3.4. Clinical and Neuropsychological assessment

All subjects underwent a detailed clinical evaluation. Socio demographics (age, gender, education), lifestyle habits (smoking, coffee and alcohol consumption, physical activity), therapeutics, routine blood tests panel mainly glucose and lipids and co-morbidities were taken. Body mass index (BMI) was calculated as weight/height (Kg/m^2); alcohol consumption was expressed as alcohol units/day (1 unit=10g alcohol) based on average alcohol content by volume of the drinks consumed (Kerr and Stockwell, 2012). Clinical diagnosis of mild dementia was confirmed by neurological and neuropsychological assessment and based on DSM classifications. The neuropsychological evaluation included the application of the Mini-Mental State Examination [MMSE; *score between 22-26* (application time: 5min)], the Clinical Dementia Rating [CDR; *score between 0.5-1* (application time: 30 min)] and the Questionnaire Subjective Memory complaints [QSM; *score from 0 to 21* (application time: 5 min)].

3.5 Experimental protocol

All the autonomic tests were performed in a dedicated laboratory, in quiet environment with controlled environmental conditions (humidity, temperature, light and noise), during the afternoon period between 4pm and 8pm, to minimize the effect of circadian changes in autonomic evaluation. Patients were instructed to have a light lunch and to refrain alcohol, tobacco, caffeine or other xanthines in the 24h before the test.

3.5.1. Autonomic evaluation

Upon arrival to the autonomic lab, patients were instructed to sit comfortably, to remain silent while breathing spontaneously. Beat-to-beat RR-intervals and arterial blood pressure were continuously monitored using a Task Force Monitor (CNSystems, Graz, Austria) during the entire testing. After an initial period of stabilization of 15 minutes, the following tests were sequentially performed leaving between them a period of stabilization of 10 minutes (Figure 2):

1st Deep metronomic breathing test (DB): the subject was instructed to breathe deeply at a rate of 6 breaths for a period of 1 min (alternating air inhalation *and* exhalation for 6 times) guided by a metronome and a visual sign.

2nd Valsalva manoeuvre (VM): subjects deep breathed and immediately blow into a tube connected to a sphygmomanometer, holding it at a pressure of 40 mmHg for 15 seconds. After this period, subjects remained seated in a resting position for 2 minutes breathing normally.

3rd Hand grip (HG): after a third resting period of 10 minutes to guarantee a stable condition, the subject performed a maximum grip with his dominant hand and the maximum capacity was noted. Then after five minutes, a grip of 30% of his maximum capacity was hold for 5 min after which it was released. The subject was instructed to breath normally during the grip in order to avoid sustained inspiration that would mimic a VM.

When a manoeuvre was not correctly performed, a period of 5 minutes was allowed to elapse and a new attempt was made.

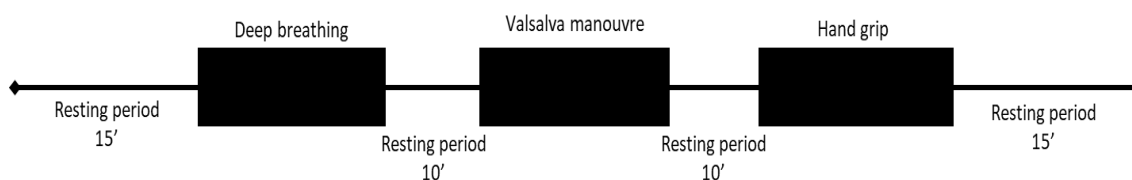


Figure 2. Timeline of the autonomic protocol showing the sequence of the performed manoeuvres.

3.6 Data analysis

3.6.1 Ewing Battery analysis

Autonomic evaluation on the time domain was performed as follows:

- *DB*: The expiratory-inspiratory ratio (E:I ratio), which is the ratio of the longest RR interval during expiration and the shortest RR interval during inspiration from 6 cycles, was calculated;
- *VM*: The Valsalva ratio derived from the longest RR interval in phase IV divided by the shortest RR interval in phase II was calculated as well as the changes on blood pressure during phase II;
- *HG*: The result of this manoeuvre is presented as the difference between the highest diastolic pressure during the examination and the average diastolic pressure at rest.

3.6.2 Cardiovascular variability

Cardiovascular variability analysis was performed in the time-scale domain through wavelet analysis using an in-house computational interface FisioSinal. The application of wavelets Db12 to autonomic evaluation allows a dynamic assessment of autonomic function with physiological significance over short periods of time with a minimum duration of 20s. After processing, the resulting spectral frequencies are: 1) low frequency power (LF; 0.04- 0.15Hz), high frequency power (HF; 0.15-0.4Hz) expressed in absolute units (mmHg² and ms², respectively).

The overall autonomic power was calculated through the relation LF/HF (mmHg²/ms²). For the assessment of overall autonomic tone, the analysis of each cardiovascular parameter, systolic blood pressure and RR intervals, was made as follows in the period of 5 minutes immediately before the deep breathing test through the evaluation of heart rate and systolic blood pressure variability. Deep breathing, Valsalva manoeuvre and hand grip were evaluated through the Ewing analysis as the irregularity of the signals did not allow the application of signal processing techniques.

3.6.3 Baroreflex Gain and Effectiveness

Baroreflex sensitivity was calculated using the sequence method as stated elsewhere (Di Rienzo *et al.*, 2001; Iacoviello *et al.*, 2011). In brief, this estimation is based on the analysis of beat-to-beat series of systolic blood pressure scanned in order to identify ramps of 3 or more consecutive heart beats with a progressive increase (up-ramp) or decrease (down-ramp), of at least 1mmHg, regardless of the possible occurrence of concomitant RR interval changes. The algorithm identifies spontaneous sequences, defined as systolic blood pressure ramps followed by concomitant and concordant RR intervals variations of 5 milliseconds coupled with 0-, 1-, and 2-beat lags, with each sequence being included only once. For each sequence, the slope of the linear interrelationship between systolic blood pressure and the following RR intervals values was calculated and was considered reliable when the correlation coefficient was greater than 0.80. For each period of analysis, the baroreflex effectiveness index is defined as the ratio between the total number of baroreflex sensitivity sequences detected and the total number of systolic blood pressure ramp-like changes in blood pressure, regardless of whether the later are followed by a change in RR-interval or not 20. The higher the effectiveness value, the more systolic blood pressure ramp changes are followed by a change in RR-interval.

3.7 Statistical analysis

Continuous variables were expressed as mean and standard error and plotted as the composite of the mean values of all subjects, unless otherwise specified. Categorical variables are given as frequencies and percentage of patients and for neuropsychological evaluation data are expressed as mean and standard deviation. Normality distribution of the continuous variables were analyzed with the Kolmogorov-Smirnov test (Lilliefors' correction) and Levene's test for assessment of homogeneity of variance. Data from different subjects - patients and controls groups - were represented along time. Student's T test was used to assess all paired data in the same group. Comparison between groups was made using a "repeated measures" analysis of variance (ANOVA) with one "within" factor (the consecutive periods of analysis) and one "between" factor (patients vs controls) with Bonferroni's correction. A value of $p < 0.05$ was considered statistically significant. Data were analyzed using SPSS software version 24 (IBM Corporation, USA).

4. RESULTS

4.1 Demographics and Neuropsychological assessment:

Many of patients were geriatric and polymorbid, which is a regular finding in dementia patients. Nevertheless, patients were divided into three groups according to their age distribution and ethnicity: AfD [50-70] years, AfD >70years and CA>70years. The CA>70 years with mild dementia was used to compare results regarding ethnicity in those patients aged >70 years. A group of afrodescendent subjects with [50-70] years without dementia was used as control of the AfD [50-70] group. Results show no significant differences between AfD [50-70] years and the control group [50-70] years and between AfD >70 years and CA>70 years in most of the factors that may potentially affect the autonomic evaluation as seen in Tables 1 and 2.

Parameter	Control group (n=12)	AfD patients (n=15)
Age (years)	64±2.6	58.6±5,8
Gender (%male)	53	33
Education (years)	10.4	7.5±4,0
BMI (Kg/m2)	30.9±1.8	27.1±1.7
Resting sBP (mmHg)	138.2±4.7	133.0±5.7
Resting dBP (mmHg)	81.1±3.6	83.0±3.5
Resting Heart rate (beats/min)	68±3.4	77.8±4.2
Number of medications	1.9±1.1	5.9±2.1
MMSE score	--	24,6±1,5
CDR score	--	0,7±0,3
QSM score	--	10,5±5,3

Table 1. Baseline demographic data for AfD mild dementia and control groups: subjects aged [50- 70] years. Continuous data are expressed in mean±SEM; categorical variables are expressed as %. Neuropsychological evaluation is expressed as mean±SD. If applicable, significant results (p<0.05) are shown in bold typeface.

Parameter	AfD patients (n=7)	CA patients (n=7)
Age (years)	79±5,7	76,6±5,3
Gender (%male)	14	14
Education (years)	4,4±2,6	4,4±2,1
BMI (Kg/m ²)	24.3±1.5	24.6±1.4
Resting sBP (mmHg)	126±8.9	124±8.2
Resting dBP (mmHg)	83±3.5	74±4.4
Resting Heart rate (beats/min)	66±3.5	70±5.4
MMSE score	23,4±1,8	24,6±1,6
CDR score	0,9±0,2	0,6±0,2
QSM score	5,7±2,6	8,1±5,3

Table 2. Baseline demographic data for AfD and CA mild dementia groups: patients aged >70 years. Continuous data are expressed in mean±SEM; categorical variables are expressed as %. Neuropsychological evaluation is expressed as mean±SD. If applicable, significant results (p<0.05) are shown in bold typeface.

For the neuropsychological evaluation, patients were also divided into two groups according to their age distribution: [50-70] years and >70 years among the afrodescendent and caucasian subjects, respectively. The results of such evaluation are depicted in accordance with the typology of the patient's groups and characteristics such as age and education (see next Tables 3, 6 and 9) and cognitive subdomains (see next Tables 4, 7 and 10 for MMSE and Tables 5, 8 and 11 for CDR).

Group I: Afrodescendents [50-70] years (n =15)

<u>Neuropsychological tests: Age & Education</u>					
	N	Minimum	Maximum	Mean	Std deviation
MMSE	15	22,00	26,00	24,6000	1,45406
CDR	15	,50	1,00	,7000	,25355
QSM	15	,00	20,00	10,4667	5,28970
Age	15	50,00	66,00	58,6000	5,79162
Education	15	,00	17,00	7,4667	3,96172
Valid N (listwise)	15				

Table 3. Neuropsychological tests; Age & Education in the [50-70] years group of Afrodescendent subjects. Data expressed as mean±SD.

From the descriptive analysis of the above table, the 15 AfD patients present a range of ages from 50 years (minimum) to 66 years (maximum) with a total age weighted average of 58,6±5,8; an educational level ranging from 0 years (minimum: illiterate) to 17 years (maximum) with a mean of 7,5±4,0; a variation in the MMSE score of 22/30 (minimum) to 26/30 (maximum) with a total weighted average of 24,6±1,5; a variation in the CDR score of 0,5/3 (minimum) to 1/3 (maximum) with a total weighted average of 0,7±0,3 and a variation in the QSM score from 0/21 (minimum) to 20/21 (maximum) with a total weighted average of 10,5±5,3.

<u>MMSE cognitive subdomains</u>					
	N	Minimum	Maximum	Mean	Std. Deviation
Orientation	15	6,00	10,00	8,6667	1,17514
Retention	15	3,00	3,00	3,0000	,00000
Atent_Calcul	15	1,00	5,00	3,6000	1,54919
Recall	15	,00	3,00	1,3333	,89974
Language	15	6,00	8,00	7,5333	,74322
Const_skill	15	,00	1,00	,4667	,51640
Valid N (listwise)	15				

Table 4. MMSE cognitive subdomains scores in the [50-70] years group of Afrodescendent subjects. Data expressed as mean±SD.

From the descriptive analysis of the above table, the 15 afrodescendent subjects presents in the MMSE subdomains scores: a range of Orientation from 6/10 (minimum) to 10/10 (maximum) with a weighted average score of 8,6±1,2; a range of mnesic Retention from 3/3 (minimum) to 3/3 (maximum) with a mean score of 3,0; a range of Attention_Calculation from 1/5 (minimum) to 5/5 (maximum) with a weighted average score of 3,6±1,5; a range of mnesic Recall from 0/3 (minimum) to 3/3 (maximum) with a weighted average score of 1,3±0,9; a range of Language competencies from 6/8 (minimum) to 8/8 (maximum) with a weighted average score of 7,5±0,7 and a range of Constructive_skills competencies from 0/1 (minimum) to 1/1 (maximum) with a weighted average score of 0,5±0,5.

<i>CDR cognitive subdomains</i>					
	N	Minimum	Maximum	Mean	Std. Deviation
Memory	15	,50	2,00	,9000	,38730
Orientation	15	,00	1,00	,6667	,36187
Judgment	15	,00	1,00	,5000	,32733
Common_affairs	15	,00	1,00	,6667	,30861
Home_Hobbies	15	,00	1,00	,4667	,39940
Personal_care	15	,00	1,00	,2667	,45774
Valid N (listwise)	15				

Table 5. CDR cognitive subdomains scores in the [50-70] years group of Afrodescendent subjects. Data expressed as mean±SD.

From the descriptive analysis of the above table, the 15 afrodescendent subjects presents in the CDR subdomains scores: a range of Memory from 0,5/3 (minimum) to 2/3 (maximum) with a mean score of 0,9±0,4; a range of Orientation from 0/3 (minimum) to 1/3 (maximum) with a mean score of 0,7±0,4; a range of Judgement (and Problem solving) from 0/3 (minimum) to 1/3 (maximum) with a mean score of 0,5±0,3; a range of Community_affairs abilities from 0/3 (minimum) to 1/3 (maximum) with a mean score of 0,7±0,3; a range of Home_Hobbies activities competencies from 0/3 (minimum) to 1/3 (maximum) with a mean score of 0,5±0,4 and lastly a range of Personal_care autonomy from 0/3 (minimum) to 1/3 (maximum) with a mean score of 0,3±0,5.

Group II: >70 years afrodescendent subjects (n =7):

<i>Neuropsychological tests: Age & Education</i>					
	N	Minimum	Maximum	Mean	Std. Deviation
MMSE	7	22,00	26,00	23,4286	1,81265
CDR	7	,50	1,00	,8571	,24398
QSM	7	3,00	10,00	5,7143	2,62769
Age	7	71,00	86,00	79,0000	5,68624
Education	7	,00	9,00	4,4286	2,63674
Valid N (listwise)	7				

Table 6. Neuropsychological tests; Age & Education in the >70 years group of Afrodescendent subjects. Data expressed as mean±SD.

From the descriptive analysis of the above table, the 7 afrodescendent subjects presents: a range of ages from 71 years (minimum) to 86 years (maximum) with a total age weighted average of 79±5,7; an educational level ranging from 0 years (minimum: illiterate) to 9 years (maximum) with a mean of 4,4±2,6; a variation in the MMSE score of 22/30 (minimum) to 26/30 (maximum) with a total weighted average of 23,4±1,8; a variation in the CDR score of 0,5/3 (minimum) to

1/3 (maximum) with a total weighted average of $0,9 \pm 0,2$ and a variation in the QSM score of 3/21 (minimum) to 10/21 (maximum) with a total weighted average of $5,7 \pm 2,6$.

<u>MMSE cognitive subdomains</u>					
	N	Minimum	Maximum	Mean	Std. Deviation
Orientation	7	8,00	10,00	9,28	,75593
Retention	7	3,00	3,00	3,00	,00000
Attention_Calc	7	1,00	5,00	2,42	1,61835
Recall	7	,00	2,00	1,00	,57735
Language	7	6,00	8,00	7,42	,97590
Construct_skill	7	,00	1,00	,28	,48795
Valid N (listwise)	7				

Table 7. MMSE cognitive subdomains scores in the >70 years group of Afrodescendent subjects. Data expressed as mean \pm SD.

From the descriptive analysis of the above table, the 7 afrodescendent subjects presents in the MMSE subdomains scores: a range of Orientation from 8/10 (minimum) to 10/10 (maximum) with a weighted average score of $9,2 \pm 0,8$; a range of mnesic Retention from 3/3 (minimum) to 3/3 (maximum) with also total weighted average score of 3,00; a range of Attention_Calculation from 1/5 (minimum) to 5/5 (maximum) with a weighted average score of $2,4 \pm 1,6$; a range of mnesic Recall from 0/3 (minimum) to 2/3 (maximum) with a weighted average score of $1,0 \pm 0,6$; a range of Language competencies from 6/8 (minimum) to 8/8 (maximum) with a weighted average score of $7,4 \pm 1,0$ and a range of Constructive_skills competencies from 0/1 (minimum) to 1/1 (maximum) with a weighted average score of $0,3 \pm 0,5$.

<u>CDR cognitive subdomains</u>					
	N	Minimum	Maximum	Mean	Std. Deviation
Memory	7	,50	1,00	,9286	,18898
Orientation	7	,00	1,00	,3571	,37796
Judgement	7	,50	1,00	,8571	,24398
Commun_affair	7	,50	1,00	,9286	,18898
Home_Hobbie	7	,50	1,00	,8571	,24398
Person_care	7	,00	1,00	,5714	,53452
Valid N (listwise)	7				

Table 8. CDR cognitive subdomains scores in the >70years group of Afrodescendent subjects. Data expressed as mean \pm SD.

From the descriptive analysis of above the table, the 7 afrodescendent subjects presents in the CDR subdomains scores: a range of Memory from 0,5/3 (minimum) to 1/3 (maximum) with a mean score of $0,9 \pm 0,2$; a range of Orientation from 0/3 (minimum) to 1/3 (maximum) with a mean score of $0,4 \pm 0,4$; a range of Judgement (and Problem solving) from 0,5/3 (minimum) to

1/3 (maximum) with a mean score of $0,9 \pm 0,2$; a range of Community_affairs abilities from 0,5/3 (minimum) to 1/3 (maximum) with a mean score of $0,9 \pm 0,2$; a range of Home_Hobbies activities competencies from 0,5/3 (minimum) to 1/3 (maximum) with a mean score of $0,9 \pm 0,3$ and lastly a range of Personal_care autonomy from 0/3 (minimum) to 1/3 (maximum) with a mean score of $0,6 \pm 0,5$.

Group II: >70 years caucasian subjects (n =7):

<u>Neuropsychological tests: Age & Education</u>					
	N	Minimum	Maximum	Mean	Std. Deviation
MMSE	7	22,00	26,00	24,5714	1,61835
CDR	7	,50	1,00	,6429	,24398
QSM	7	1,00	15,00	8,1429	5,33631
Age	7	71,00	82,00	76,5714	5,28700
Education	7	3,00	9,00	4,4286	2,07020
Valid N (listwise)	7				

Table 9. Neuropsychological tests; Age & Education in the >70 years group of Caucasian subjects. Data expressed as mean \pm SD.

From the descriptive analysis of above table, the 7 caucasian subjects presents: a range of *ages* from 71 years (minimum) to 862 years (maximum) with a total *age* weighted average of $76,6 \pm 5,3$; an *educational* level ranging from 3 years (minimum) to 9 years (maximum) with a mean of $4,4 \pm 2,1$; a variation in the *MMSE score* of 22/30 (minimum) to 26/30 (maximum) with a total weighted average of $24,6 \pm 1,6$; a variation in the *CDR score* of 0,5/3 (minimum) to 1/3 (maximum) with a total weighted average of $0,6 \pm 0,2$ and a variation in the *QSM score* of 1/21 (minimum) to 15/21 (maximum) with a total weighted average of $8,1 \pm 5,3$.

<u>MMSE cognitive subdomains</u>					
	N	Minimum	Maximum	Mean	Std.Deviation
Orientation	7	5,00	10,00	8,5714	1,71825
Retention	7	3,00	3,00	3,0000	,00000
Atention_Calcu	7	2,00	5,00	3,2857	1,11270
Recall	7	,00	3,00	1,2857	1,11270
Language	7	8,00	8,00	8,0000	,00000
Const_skill	7	,00	1,00	,4286	,53452
Valid N (listwise)	7				

Table 10. MMSE cognitive subdomains scores in the >70 years group of Caucasian subjects.

From the descriptive analysis of the above table, the 7 caucasian subjects presents in the MMSE subdomains scores: a range of Orientation from 5/10 (minimum) to 10/10 (maximum) with a weighted average score of $8,5 \pm 1,7$; a range of mnesic Retention from 3/3 (minimum) to 3/3

(maximum) with also a total weighted average score of 3,00; a range of Attention_Calculation from 2/5 (minimum) to 5/5 (maximum) with a weighted average score of 3,2±1,1; a range of mnesic Recall from 0/3 (minimum) to 3/3 (maximum) with a weighted average score of 1,2±1,1; a range of Language competencies from 8/8 (minimum) to 8/8 (maximum) with also a weighted average score of 8,00 and a range of Constructive_skills competencies from 0/1 (minimum) to 1/1 (maximum) with a weighted average score of 0,4±0,5. Data expressed as mean±SD.

<i>CDR cognitive subdomains</i>					
	N	Minimum	Maximum	Mean	Std. Deviation
Memory	7	,50	1,00	,9286	,18898
Orientation	7	,50	1,00	,7143	,26726
Judgement	7	,00	1,00	,5000	,28868
Commun_affairs	7	,00	1,00	,5000	,40825
Home_Hobbie	7	,50	1,00	,7143	,26726
Personal_care	7	,00	1,00	,1429	,37796
Valid N (listwise)	7				

Table 11. CDR cognitive subdomains scores in the >70 years group of Caucasian subjects. . Data expressed as mean±SD.

From the descriptive analysis of the above table, the 7 caucasian subjects presents in the CDR subdomains scores: a range of Memory from 0,5/3 (minimum) to 1/3 (maximum) with a mean score of 0,9±0,2; a range of Orientation from 0,5/3 (minimum) to 1/3 (maximum) with a mean score of 0,7±0,3; a range of Judgement (and Problem solving) from 0,5/3 (minimum) to 1/3 (maximum) with a mean score of 0,5±0,3; a range of Community_affairs abilities from 0/3 (minimum) to 1/3 (maximum) with a mean score of 0,5±0,4; range of Home_Hobbies activities competencies from 0,5/3 (minimum) to 1/3 (maximum) with a mean score of 0,7±0,3 and lastly a range of Personal_care autonomy from 0/3 (minimum) to 1/3 (maximum) with a mean score of 0,1±0,4

The summary of these main results is shown on Tables 12, 13 and 14 below:

Patients	Subjects (n)	MMSE (score)	CDR (score)	QSM (score)	Age (years)	Education years (years)
Group I AfD	15	24,6±1,5	0,7±0,3	10,5±5,3	58,6±5,8	7,5±4,0
Group II AfD	7	23,4±1,8	0,9±0,2	5,7±2,6	79±5,7	4,4±2,6
Group II CA	7	24,6±1,6	0,6±0,2	8,1±5,3	76,6±5,3	4,4±2,1

Table 12. Neuropsychological tests; Age & Education means scores between Patients-groups (Group I AfD: [50-70] years afrodescendent subjects; Group II AfD: >70 age afrodescendent subjects; Group II CA: >70 years caucasian subjects). Data expressed as mean±SD.

The MMSE average score was inferior in the Group II AfD and were similar between Group

I AfD and Group II CA. The CDR average score was inferior in the Group II CA and higher in the Group II AfD. The QSM average score was higher in the Group I AfD then in Group II CA and lower for Group II AfD. Finally, we refer in this context to *age* and *education* because they are demographic variables that may influence the performance in neuropsychological tests. The Group II AfD presents the higher average *age* between patients groups (79±5,7); Group II CA (76,6±5,3) is the second group with older subjects and the Group I AfD is where the lowest average age of patients is concentrated (58,6±5,8).

Regarding the *education* level there is a similar average years of education between Groups II- AfD (4,4±2,6) and II-CA (4,4±2,1), and the Group I AfD is the one that has the higher education average level (7,5±4,0). In a qualitative analysis there does not seem to be much disparity between the average neuropsychological scale scores (MMSE; CDR and QSM) since they were defined for the study as measures of inclusion criteria. But, on the other hand, it seems to be more evident that the group with the lowest average age (Group I AfD: [50- 70] years afrodescendent subjects) corresponds to a higher educational level and that the groups with the most advanced ages (Group II AfD: >70 years afrodescendent subjects; Group II CA: >70 years caucasian subjects) correspond to a lower educational level.

Patients	Subjects (n)	MMSE cognitive subdomains					
		Orientation (score)	Retention (score)	Attent.+Calc. (score)	Recall (score)	Language (score)	Construct_ skill (score)
Group I AfD	15	8,7±1,2	3,00	3,6±1,5	1,3±0,9	7,5±0,7	0,5±0,5
Group II AfD	7	9,3±0,8	3,00	2,4±1,6	1±0,6	7,4±1	0,2±0,5
Group II CA	7	8,6±1,7	3,00	3,3±1,1	1,3±1,1	8,0±0,0	0,4±0,5

Table 13. MMSE cognitive subdomains* means scores between patients-groups (Group I AfD: [50-70]age afrodescendent subjects; Group II AfD: >70 age afrodescendent subjects; Group II CA: >70 age caucasian subjects); *scores Orientation: 0-10; Retention: 0-3; Attention&Calculation: 0-5; Recall: 0-3; Language: 0-8 and Constructive_skills:0-1. Data expressed as mean±SD.

Table 13 summarizes the previous MMSE cognitive subdomains scores. In Orientation all patient's groups (Groups I-AfD; II-AfD and II-CA) seems to have a similar average performance but the Group II AfD (>70 age caucasian subjects) has the higher average score in this subdomain (9,3±0,8). In the *Retention* subdomain there is no difference between groups (3,00).

In the *Attention and Calculation* task the Group I AfD as the higher average score (3,6±1,5)

then was the Group II CA ($3,3\pm1,1$) and Group II AfD ($2,4\pm1,6$). In the *Recall* subdomain Groups I-AfD and II-CA have almost the same (average score: $\pm1,3$) and the Group II AFD has the lower mean score ($1\pm0,6$). The *Language* competence was similar between Group I AfD ($7,5\pm0,7$) and Group II AfD ($7,4\pm1$), and higher in the Group II CA ($8,00$). Regarding the *Constructive skills* one more time all the 3 patients-groups seems to have the same average score (Group I AfD: $0,5\pm0,5$; Group II AfD: $0,2\pm0,5$ and Group II CA: $0,4\pm0,5$). From the qualitative analysis, the most evident differences in mean results are found in the median subdomains of evocation and orientation, and these seem to be the ones that most influenced the total mean MMSE scores between the patient groups. Data expressed as mean \pm SD.

Patients	Subjects (n)	CDR cognitive subdomains					
		Memory (score)	Orientation (score)	Judg& ProbS (score)	C_affairs (score)	Home&Hob. (score)	Personal_care (score)
Group I AfD	15	$0,9\pm0,4$	$0,7\pm0,4$	$0,5\pm0,3$	$0,7\pm0,3$	$0,5\pm0,4$	$0,3\pm0,5$
Group II AfD	7	$0,9\pm0,2$	$0,4\pm0,4$	$0,9\pm0,2$	$0,9\pm0,2$	$0,9\pm0,2$	$0,6\pm0,5$
Group II CA	7	$0,9\pm0,2$	$0,7\pm0,3$	$0,5\pm0,3$	$0,5\pm0,4$	$0,7\pm0,3$	$0,1\pm0,4$

Table 14 CDR cognitive subdomains* means scores between Patients-groups (Group I AfD: [50-70] years afrodescendent subjects; Group II AfD: >70 years afrodescendent subjects; Group II CA: >70 years caucasian subjects); *(Memory; Orientation; Judgement&Problem Solving; Community_affairs; Home&Hobbies and Personal_care, all sub-scores between 0; 0,5; 1; 2 or 3 qualitative classification sum of boxes). Data expressed as mean \pm SD.

Table 14 resumes the previous CDR cognitive subdomains results score. The CDR subdomains score is not a continuum variable because it's a qualitative attributive score that variates between 0 (*no dementia*); 0,5 (*suspected dementia*); 1(*mild dementia*) and 2(*moderate dementia*) and 3 (*severe dementia*), based on a qualitative clinical-inter- view with some neuropsychological tasks. The difference to the MMSE or QSM scores is that in CDR a higher score corresponds to a higher cognitive and functional impairment. As we can analyze de *Memory* subdomain was almost the same for the 3 patients-group (mean score: $\approx0,9$).

The Groups I-AfD and II-CA had the higher mean score in the *Orientation* questions ($0,7\pm0,4$ and $0,7\pm0,3$ respectively) and the Group II AfD ($0,4\pm0,4$) had the lower score. In the Judgement & Problem_solving neuropsychological tasks the Group II AfD had the higher mean value ($0,9\pm0,2$) and the Groups I AfD and II CA the same result ($0,5\pm0,3$). The

Community_affairs subdomain was higher punctuated by the patients of Group II AfD ($0,9\pm0,2$), then less punctuated by Group I AfD ($0,7\pm0,3$) and in the end with less mean score by the Group II CA ($0,5\pm0,4$). The Group II achieved a higher mean score in *Home&Hobbies* category with $0,9\pm0,2$ of the results, then the Group II CA with $0,7\pm0,3$ scores and at a lower position average the Group I AfD with $0,5\pm0,4$. At last the *Personal_care* subdomain was much higher in Group II AfD then in Group I AfD ($0,3\pm0,5$) and with the lowest mean score the Group II CA ($0,1\pm0,4$). In the *Orientation* all the patient's groups (Groups I-AfD; II-AfD and II-CA) seem to have a similar average performance but the Group II A (>70 age caucasian subjects) had the higher average score in this subdomain ($9,3\pm0,8$). In the *Retention* subdomain there is no difference between groups (3,00).

In the *Attention and Calculation* task the Group I AfD had the higher average score ($3,6\pm1,5$) then was the followed by Group II CA ($3,3\pm1,1$) and the Group II AfD ($2,4\pm1,6$). In the *Recall* subdomain the Groups I-AfD and II-CA had almost the same average score (1,3) and the Group II AfD as the lower mean score ($1\pm0,6$). The *Language* competence was similar between Group I AfD ($7,5\pm0,7$) and Group II AfD ($7,4\pm1$), and higher in the Group II CA (8,00). Regarding the *Constructive skills*, again all the 3 patients-groups seems to have the same average score (Group I AfD: $0,5\pm0,5$; Group II AfD: $0,2\pm0,5$ and Group II CA: $0,4\pm0,5$). From the qualitative analysis, the most evident differences in mean results are found in the median subdomains of evocation and orientation, and these seem to be the ones that most influenced the total mean MMSE scores between the patient groups. From the qualitative analysis, the most evident differences in mean results it seems to be found in the *Community_affairs*; *Home&Hobbies* and *Personal_care* between the patient groups. Data expressed as mean \pm SD.

4.2 Autonomic Evaluation

4.2.1 Cardiovascular variability

Systolic, diastolic arterial pressures and heart rate, at rest, were not different in all groups. Regarding autonomic evaluation, our results show that all patients have a lower autonomic tone comparing with controls Table 15. In particular, LF and HF show statistically significant differences between the three groups (Figs.: 3-5). Regarding general autonomic tone, there is a tendency for a decrease with age (Figure 5) with the afrodescendent patients having a higher tone than the Caucasians which is in line with the values of resting systolic blood pressure (Tables 15 and 16).

Parameter	LF (mmHg ²)	HF (ms ²)	LF/HF
AfD [50-70] years	1,80±0,202	32,37±7,430	0,09±0,017
AfD >70years	1,18±0,303	25,69±5,549	0,07±0,027
CA >70 years	1,12±0,239	39,95±7,007	0,05±0,023
Control group	3,6±0,86	94±29,1	2,6±0,55

Table 15. Values of overall power spectral analysis of heart rate and blood pressure variability in the evaluated group of subjects. Control group (n=12); CA>70 and AfD>70 (n=7); AfD [50-70] (n=15).

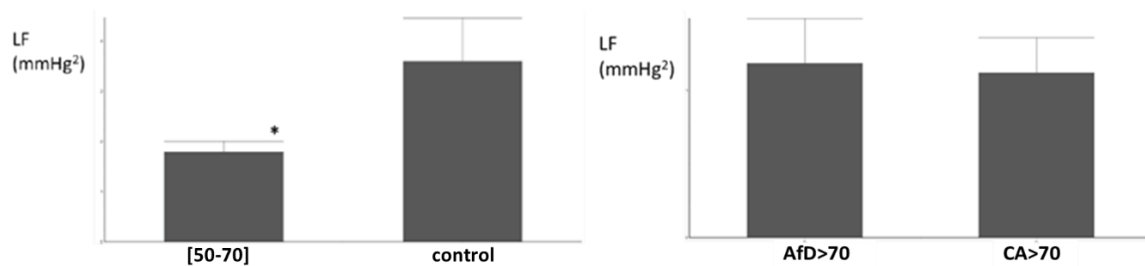


Figure 3. Comparison of LF power band power, an indication of resting sympathetic activity, between the evaluated groups.

Afrodescendent (AfD) and Causasian (CA) patients, all aged >70, do not show significant changes on sympathetic flow. Younger patients [50-70] have a lower autonomic tone when compared with matching controls, the same been observed to aged CA patients while for AfD patients the differences to controls are not quite significant probably due to the small sample size. *significant between the indicated group and control ($p>0.05$). Data expressed as mean±SEM.

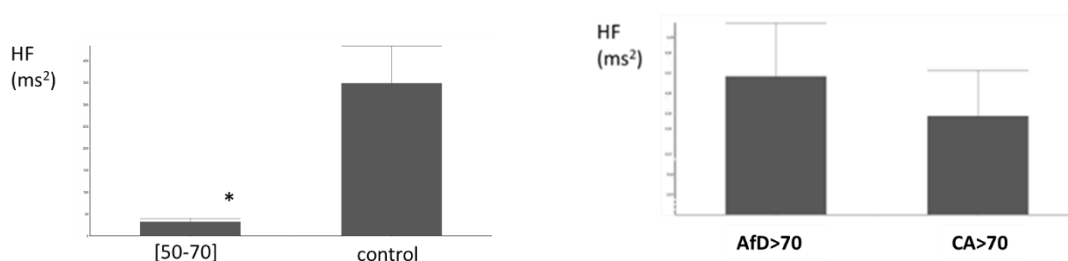


Figure 4. Significant differences were observed on parasympathetic tone between the patient's groups and the control.

Nevertheless, among AfD and AC groups, both aged >70, the parasympathetic outflow was of similar magnitude. Between these two groups and despite the age factor which usually impacts autonomic evaluation, parasympathetic tone was also not significantly different. * significant between the indicated group and control ($p > 0.05$). Data expressed as mean \pm SEM.

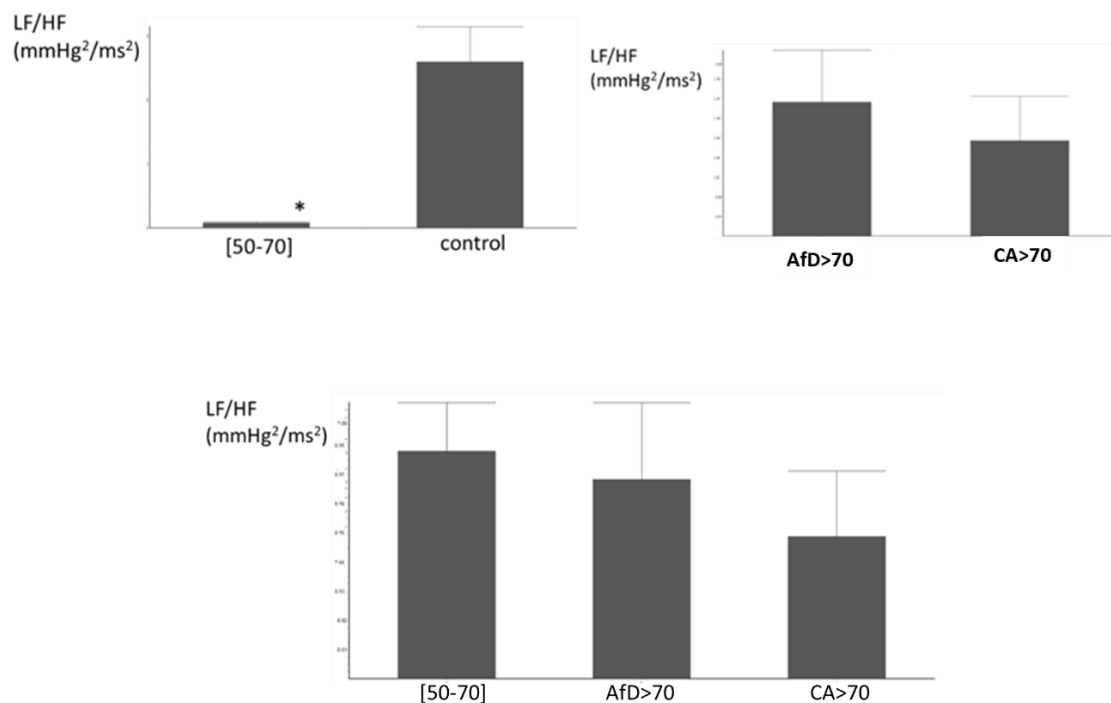


Figure 5. Autonomic outflow is significantly reduced in all groups of patients independently of age. A tendency is observed for a higher autonomic tone among AfD patients independently of the age regarding the CA ones which is in line with blood pressure values at rest. * significant between the indicated group and control ($p > 0.05$). Data expressed as mean \pm SEM.

4.2.2 Baroreceptor reflex study

The evaluation of baroreflex sensitivity or gain (BRS) and its effectiveness (BEI) using the sequence method demonstrates an impairment of baroreceptor function in all patient groups (Table 16) without any significance difference between them. Baroreflex receptor, despite present, shows a delayed response with 100% of all spontaneous baroreflex sequences occurring at lag 2 for all groups of patients when compared with controls.

	[50-70] years	DA>70 years	CA>70 years	Control
BEI (%)	32,8±13,3	32,5±12,5	28,2±15,3	70±1,5
BRS (ms/mmHg)	5,1±3,4	5,2±3,5	6±1,6	19,1±1,6

Table 16. Values for BEI and BRS for all groups of patients and controls. [50-70] years, n=9; DA>70, n=6; CA>70, n=6. Data are presented as mean±SEM.

4.2.3 Autonomic provocative manoeuvres

Regarding the autonomic manoeuvres, not all the patients were able to perform them at all while others had a deficient performance. Both the difficulty of communication as well the age of the patients are reasons for that absence of performance which has consequences on data recording and analysis. Nevertheless, the manoeuvre which was better performed was deep breathing probably, and beyond the reasons already expressed, because it was the first manoeuvre of the evaluation protocol. Thus, results for the 3 manoeuvres-deep breathing, Valsalva manoeuvre and handgrip- are presented just as an example.

4.2.3.1 Deep Breathing test

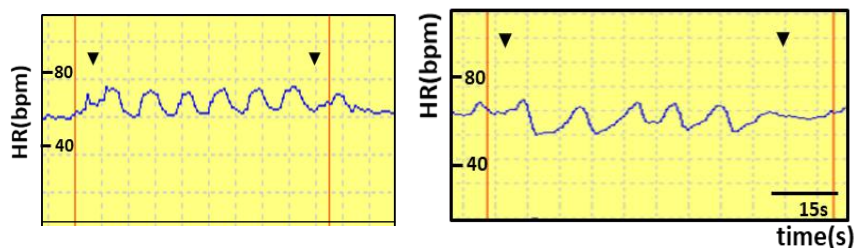
The deep breathing test is a predominantly parasympathetic manoeuvre as it evaluates heart rate responses to changes on respiratory rate being based on the physiological mechanism underlying respiratory sinus arrhythmia.

According to the Ewing testing it is analyzed through the changes of heart rate during the manoeuvre. An expiratory/inspiratory (E/I) index

$$EI = \sum [HR_{\max} - HR_{\min}/\text{cycle}] / 6$$

is calculated as if E/I >15, the test is normal but if E/I <15 indicates an impairment of parasympathetic system. Representative examples of deep breathing area shown in Figure 6 (A and B), below.

A.



B.

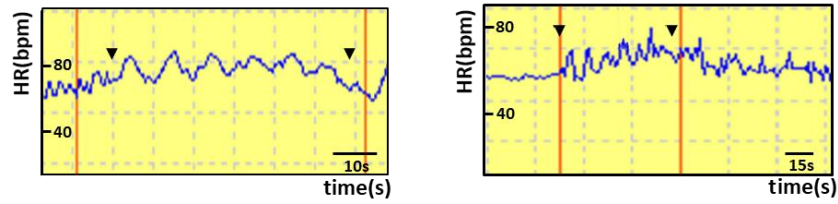


Figure 6. Deep metronomic breathing of four afrodescendent patients extracted from the recordings of two patients of each group: [50-70] years (A) and >70 years groups (B).

Where can be observed the difference in the test performance which is age-related but not related to the neuropsychological scores. The E/I calculation for [50-70] years is 16,6 and 10 respectively for the left and right patient indicating a normal and impaired parasympathetic outflow. For the patients >70 years old, an increase in the baseline heart rate is observed during the test due to the difficulty in performing the test, purpose that wasn't accomplished by the last patient. Indicates the actual starting and end of the test. Red lines are indicative markers inserted during the evaluation.

4.2.3.2 Valsalva Manoeuvre

Valsalva manoeuvre (VM) assesses heart rate and blood pressure changes due to baroreflex changes evoked by a respiratory strain. It comprises four phases, two mechanical (I and III) and two reflex ones (II and IV). VM is evaluated through the Valsalva Ratio which is expressed as

$$V_R = \frac{HR_{\max / \text{phase II}}}{HR_{\min / \text{phase IV}}}$$

The response to VM is normal if $VM > 1$ and abnormal otherwise.

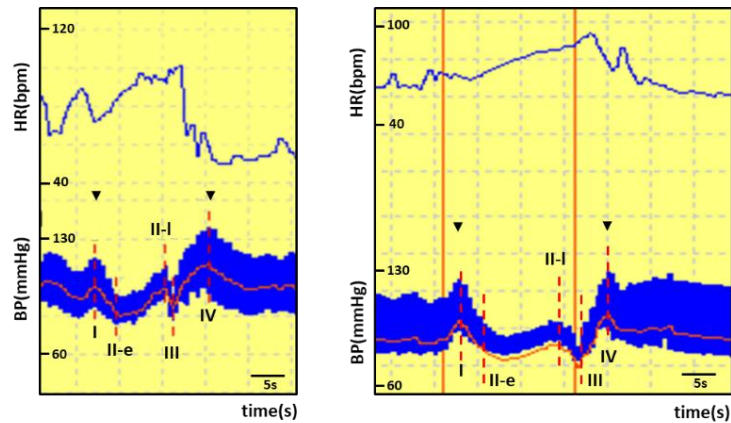


Figure 7. The Valsalva manouvre performed by a patient from the [50-70] group (right panel) with a VR=1,1 and BP changes. On the left, an example of a slightly longer manouvre that was performed by some patients due probably to age and/or difficulty in understanding the given instructions.

Regarding the BP changes during VM related to the adrenergic control, it could be observed that BP in phase III has values below the resting level indicating an impairment of sympathetic activity due to baroreflex dysfunction. Also, despite the normal value of VM, some patients also performed the manouvre in a slight longer time. Data shows the presence of all the Valsalva phases nevertheless the time for the completion of the manouvre is longer than standard 15s used by a control patient. The Valsalva manouvre encompasses four phases, two of them due to mechanical effects (I and III) corresponding to the increase and decrease of intrathoracic pressure; the other two, are of reflex origin (II and IV); phase II is further subdivided into II-e (earlier phase II) when the cardiac output is reduced and the increased intrathoracic pressure blocks the venous return to the heart, and phase II-l (late phase II) which expresses baroreflex activation, indicates the actual starting and end of the test. Red lines are indicative markers inserted during the evaluation.

4.2.3.3 Hand-Grip

The hand grip test (HG) is a predominantly sympathetic manouvre as it evaluates sympathetic activation due to the increase of metabotropic muscle receptors under an isometric contraction. A normal manouvre evokes, at least, an increase of 20mmHg in diastolic blood pressure and 10bpm in heart rate.

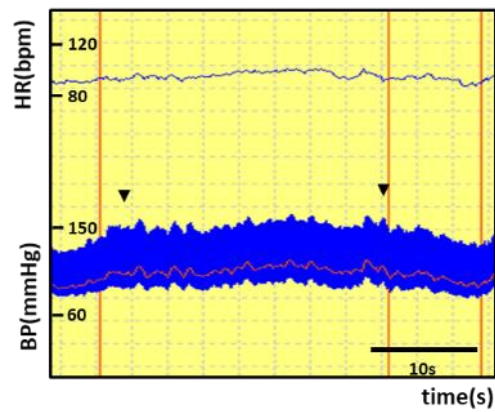
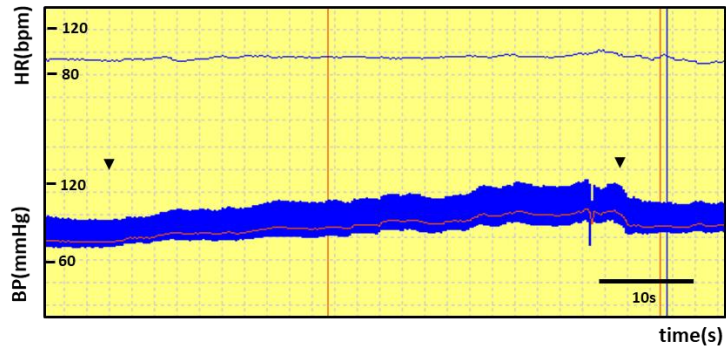


Figure 8. In this figure are shown two HG performed by [50-70] years patient (top) and by a patient AfD>70 years (bottom).

While the top manoeuvre has a normal profile, the lower one is revealing a sympathetic impairment due to a deficient rise in diastolic blood pressure with the arrows indicating the actual starting and end of the test.

5. DISCUSSION

Both on clinics and in research, autonomic evaluation through power spectral analysis is widely used as a way to qualify and quantify autonomic function. In fact, it has been shown that the two main spectral frequencies – low and high frequencies (LF and HF) correlate well with the autonomic tone to the periphery. Indeed, LF is influenced by mainly the sympathetic tone whereas HF is a quantitative marker of parasympathetic function also being influenced by the respiratory rate. The ratio of LF and HF is recognized as the balance of sympathetic and parasympathetic activity and represents the overall autonomic tone.

The present pilot study is the first in Portugal addressing the autonomic function in a minority population - the afrodescendent population- suffering from mild dementia. Despite being a pilot study, our results show a pathologic pattern in the autonomic regulation in these patients evaluated through signal processing and Ewing battery of tests. Indeed, a decreased autonomic tone as a consequence of a lower sympathetic and parasympathetic together with an impaired baroreflex function was observed.

Overall, our results are in line with previous already published in afro-american populations (Liao et al, 1995; Calhoun et al, 1993) with HF and LF/HF ratio being higher in afro descendant patients despite having a cognitive impairment, but LF values are varying in an opposite way (Giubilei et al, 1998; Zulli et al, 2005; de Vilhena Toledo and Junqueira, 2008). Despite believing that this is a novel result as it comes in line with a recent published work of Struhal and co-workers in caucasian patients with dementia and neurodegenerative disease (Struhal et al, 2016) we may also consider that some of the reasons for this dissonant result may be related to the disease itself, to the age of the patients, to a different methodology of evaluation, to the patient's therapeutics or to our small sample size or a combination of a few or all of these factors. The reasons why these differences are expressed are not yet known but from our study as well from similar ones, it is reinforced that race and age needs to be considered when assessing autonomic function.

In our study, we used two different ways of evaluating autonomic testing: a time-scale analysis of a basal period and provocative manoeuvres and we noticed that, for this population of patients, the former was more effective in collecting autonomic information than the second. Indeed, Valsalva maneuver, deep breathing and handgrip need a high degree of motivation and cooperation from the patients which may be difficult in aged and dement patients even with mild presentations, thus leading to a strong study limitation of autonomic function with provocation in this type of patients to avoid false results, results

with no consequence and a high rate of drop-outs. In fact, by using signal processing independently of the provocative manoeuvres, we were able to show differences between the autonomic behavior of the evaluated patients and the controls which is in opposition to Nicolini et al (2016) who didn't find significant differences in mild cognitive patients when autonomic evaluation was performed in baseline conditions.

Baroreflex gain or sensitivity (BRS) allows to qualify and quantify the reflex circulatory effects which are due to baroreceptor activation on inhibition being an indirect way of, through an autonomic reflex, indirectly evaluate the full system. In the present study, we observed a reduced baroreceptor responsiveness accompanying mild dementia. BRS was evaluated through the sequence method which is based on the spontaneous presence of concurrent RR intervals and systolic blood pressure changes (increase or decrease) over three consecutive heartbeats. This method allows the assessment of two complementary parameters regarding the baroreceptor control of circulation: one, the BRS qualifies the information about the baroreceptor sensitivity through the measurement of the reflex changes in RR interval in respect to systolic blood pressure reflex changes whereas the second, the baroreflex effectiveness index – BEI – gives quantitative information on baroreflex function by calculating the number of times the baroreflex is effective in driving the sinus node (Di Rienzo et al, 2001; Iacoviello et al, 2008, 2010). In comparison with other indirect methods of autonomic evaluation, BRS offers a higher reproducibility in comparison with stimulus-dependent methods (mainly with intravenous drugs), it is not dependent from the operator and a dynamic assessment of the baroreceptor reflex in short periods (LaRovere et al, 2008). It has been previously shown that in response to a quick change in blood pressure the relationship between systolic blood pressure and RR-intervals is linear. In our study, it was observed a shift of the sequences to lag-2 indicating a strong delay in the chronotropic response and suggesting a putative activation of the slow sympathetic activation with the deactivation of the fast-vagal response (Malliani, 200; Nollo et al, 2005). If these functional changes are due to the disease itself which might be affecting crucial brain stations of the central autonomic network or a consequence of patient's therapeutics and co-morbidities which were not discontinued during our study, is still a subject of debate which requires further investigation. Some studies on autonomic responses to orthostasis have suggested that an impaired baroreflex elicits abnormal sympathetic and para-sympathetic responses to orthostasis (Mosqueda Garcia et al, 1996).

In line with these results, we may hypothesize that, in our study, the baroreflex impairment is strongly related to the decrease in autonomic function but mainly in sympathetic activity as was observed in autonomic evaluation in the basal period as well as through the delay of the Valsalva manoeuvre and the small rise of diastolic blood pressure during hand grip. However, since we worked with a reduced sample size, we need to be cautious regarding this hypothesis. The relation between baroreflex and cognition has also been studied. In fact, previous studies (Yasumasu et al., 2006) show that baroreceptor reflex (BR) sensitivity is inhibited during a cognitive performance, and the level of this baroreceptor inhibition was negatively and significantly associated with the degree of cognitive performance during mental load stress tasks. This supports the existence of a pathway loop mediating mutual cardiovascular-central nervous system influences through the baroreceptors, and this interaction may be a dynamic mechanism of fundamental importance for cardiovascular regulation and an essential mechanism supporting adaptive reactions to stressful conditions. In our study we evaluated cognitive measures with neuropsychological tools for the inclusive criteria of both afrodescendent and caucasian patients. Another previously and specific study suggested that baroreceptor reflex sensitivity is more sensitive to internal cognitive elaboration conditions, while baroreflex effectiveness index is more sensitive to external attention conditions (del Paso; González & Hernández, 2004). These suggestions are in line with our results where a generalized decreased cognitive function is associated to baroreflex impairment (both BRS and BEI) and autonomic dysfunction. Whereas BRS and /or BEI may be used as marker of therapeutic effectiveness is still a matter of debate but some studies already gave some hints on this possibility. In particular, Meelvan and co-workers suggested BRS as a valid biomarker between cardiovascular disease and AfD (Meel-van et al., 2013), because BR is reduced in Alzheimer disease and is influenced by autonomic effects of cholinesterase inhibitors (ChEI). These studies have also shown that ChEI treatment induced a 66% in BR in Alzheimer patients (Meel-van et al., 2013). Also regarding cognitive functions and autonomic function in MCI patients, an early prodromic phase of dementia, acetylcholine the main neurotransmitter of the para-sympathetic system may be deficient, besides the components of the central autonomic network attract the greatest neurofibrillary degeneration and related cell death during the course of AfD and the insular cortex and brainstem are affected from the early stages of the disease (Collins *et al.*, 2012).

For all these reasons we also believed that further investigation is need to useful despite the autonomic dysfunction as a biomarker of neurodegeneration and provides insight into the pathophysiological mechanisms that contribute to cognitive decline and may lead to the development of effective therapeutic interventions.

In a descriptive and qualitative analysis of the neuropsychological data used as a clinical reference for the inclusion of our subjects, we observed that in both group-age of patients ([50-70] and >70years) the score average obtained in MMSE; CDR and QSM were indicative of higher functional impairments in cognitive subdomains in the afrodescendent patients compared to whites subjects. Especially this mean relation score among the younger age [50-70] grouping. In other words, the afrodescendent patients included in this study presented the lowest performance in memory and orientation tasks and a higher prevalence of self-perceived mnesic and executive complaints during their daily activities living.

6. CONCLUSIONS

Regardless being a pilot study, to the best of our knowledge this is the first study based on a comprehensive autonomic evaluation by signal processing methodologies and Ewing battery manouvres to show autonomic dysfunction, mainly due to the lack of parasympathetic reserve, together with a baroreflex impairment in afrodescendent patients, non Caucasian, with mild dementia in Portugal.

Despite out of the scope of our work, it might be hypothesized that alterations in the central autonomic network beyond those resulting from the aging process, might be underlying the observed results. The importance of these results lies on the fact that baroreflex and autonomic impairments may be related with the progression of the disease or be an inductor of co-morbidities including cardiovascular and orthostatic intolerance which may lead to falls, dizziness or even syncopal events in these patients. Also, BRS and /or BEI may be considered as valid biomarkers of disease progression of therapeutic effectiveness but further research is still needed. Regarding the neuropsychological measures associated with the autonomic evaluation of these patients, it would be interesting in future investigations with similar methodologies to apply a neuropsychological evaluation protocol not only to include or exclude participants based on clinical criteria but to perform a more thorough diagnosis at two times, for example (before and after) the autonomic evaluation. In this approach it would be also interesting to explore perhaps physiological measures associated with emotional states and depressive symptoms; Stress levels or fears and cultural life habits related to better characterize and clinical support this Portuguese afrodescendent population from the national healthcare system of the municipalities of Amadora and Sintra.

6.1 Study limitations

The present study has various limitations some of which may be overcome within further work. The most relevant is the sample size. In fact, despite a larger period of sensitization and information of the community about the project to facilitate the recruitment of patients and their healthy relatives to incorporate a control group, our efforts were somewhat unsuccessful. Nevertheless, the acquired knowledge on the dynamics of the minority and vulnerable communities will allow to better delineate new studies overcoming this limitation.

7. REFERENCES

- Aguirre, E., Woods, R. T., Spector, A., & Orrell, M. (2013). Cognitive stimulation for dementia: a systematic review of the evidence of effectiveness from randomized controlled trials. *Ageing Research Reviews*, 12(1), 253-262
- Aharon-Peretz, J., Harel, T., Revach, M., & Ben-Haim, S. A. (1992). Increased sympathetic and decreased parasympathetic cardiac innervation in patients with Alzheimer's disease. *Archives of Neurology*, 49(9), 919-922
- Ainsworth, B. E., Haskell, W. L., Herrmann, S. D., Meckes, N., Bassett Jr, D. R., TudorLocke, C., ... & Leon, A. S. (2011). 2011 Compendium of Physical Activities: a second update of codes and MET values. *Medicine, Science in Sports & Exercise*, 43(8), 1575- 1581
- Alabdulgader, A. A. (2012). Coherence: a novel nonpharmacological modality for lowering blood pressure in hypertensive patients. *Global Advances in Health and Medicine*, 1(2), 56-64
- Algotsson, A., Viitanen, M., Winblad, B., & Solders, G. (1995). Autonomic dysfunction in Alzheimer's disease. *Acta Neurologica Scandinavica*, 91(1), 14-18
- Allan, L. M., Ballard, C. G., Allen, J., Murray, A., Davidson, A. W., McKeith, I. G., & Kenny, R. A. (2007). Autonomic dysfunction in dementia. *Journal of Neurology, Neurosurgery & Psychiatry*, 78(7), 671-677
- Allan, L. M., Kerr, S. R. J., Ballard, C. G., Allen, J., Murray, A., McLaren, A. T., & Kenny, R. A. (2005). Autonomic function assessed by heart rate variability is normal in Alzheimer's disease and vascular dementia. *Dementia and Geriatric Cognitive Disorders*, 19(2-3), 140-144.
- Allan, L. M., Kerr, S. R. J., Ballard, C. G., Allen, J., Murray, A., McLaren, A. T., & Kenny, R. A., Vasquez, E., Mayorga, C. C., Feaster, D. J., & Mitrani, V. B. (2006). Increasing minority research participation through community organization out- reach. *Western Journal of Nursing Research*, 28(5), 541-560
- Alzheimer's Association. (2010). 2010 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, 6(2), 158-194

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub

Anderton, B. H. (1987). Alzheimer's disease. *Progress in Molecular Pathology. Nature* 325, 658-659

Ardell, J. L., Butler, C. K., Smith, F. M., Hopkins, D. A., & Armour, J. A. (1991). Activity of in vivo atrial and ventricular neurons in chronically decentralized canine hearts. *American Journal of Physiology-Heart and Circulatory Physiology*, 260(3), H713-H721

Ardell, J. L., Cardinal, R., Vermeulen, M., & Armour, J. A. (2009). Dorsal spinal cord stimulation obtunds the capacity of intrathoracic extracardiac neurons to transduce myocardial ischemia. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 297(2), R470-R477

Armour, J. A. (1991). Intrinsic cardiac neurons. *Journal of Cardiovascular Electrophysiology*, 2(4), 331-341

Armour, J. A. (2003). Neurocardiology. *Anatomical and Functional Principles*. Boulder Creek, CA: HeartMath Research Center, Institute of HeartMath, Publication, (03- 011)

Armour, J. A. (2008). Potential clinical relevance of the 'little brain' on the mammalian heart. *Experimental physiology*, 93(2), 165-176

Armour, J. A., & Ardell, J. L. (Eds.). (2004). *Basic and Clinical Neurocardiology*. Oxford University Press

Ballard, C., Shaw, F., McKeith, I., & Kenny, R. (1998). High prevalence of neurovascular instability in neurodegenerative dementias. *Neurology*, 51(6), 1760-1762

Banerjee, S. (2010). Living well with dementia-development of the national dementia strategy for England. *International Journal of Geriatric Psychiatry*, 25(9), 917- 922

Barnes, L. L., & Bennett, D. A. (2014). Alzheimer's disease in African Americans: risk factors and challenges for the future. *Health Affairs*, 33(4), 580-586

Barnes, L. L., Leurgans, S., Aggarwal, N. T., Shah, R. C., Arvanitakis, Z., James, B. D., ... & Schneider, J. A. (2015). Mixed pathology is more likely in black than white decedents with Alzheimer dementia. *Neurology*, 85(6), 528-534

Beauchaine, T. (2001). Vagal tone, development, and Gray's motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. *Development and Psychopathology*, 13(2), 183-214

Beaumont, J. G. (2008). *Introduction to Neuropsychology*. Guilford Press

Bedell, W., & Kaszkin-Bettag, M. (2010). Coherence and healthcare cost-RCA actuarial study: a cost-effectiveness cohort study. *Congestive Heart Failure*, 21,22

Bennett, D., A Schneider, J., S Buchman, A., L Barnes, L., A Boyle, P., & S Wilson, R. (2012). Overview and findings from the rush Memory and Aging Project. *Current Alzheimer Research*, 9(6), 646-663

Berntson, G. G., Norman, G. J., Hawkley, L. C., & Cacioppo, J. T. (2008). Cardiac autonomic balance versus cardiac regulatory capacity. *Psychophysiology*, 45(4), 643- 652

Borson, S., Lampe, T., Raskind, M. A., Veith, R. C., Morely, J. E., Coe, R. M., ... & Gross- berg, G. T. (1992). Autonomic nervous system dysfunction in Alzheimer's disease: Implications for pathophysiology and treatment. In *Memory Function in Aging and Age-Related Disorders* (pp. 175-189). Springer Publishing Co New York

Bourscheid, F.R., Mothes, L., & Irigaray, T. Q. (2016). Memory in the elderly: relationship between subjective perception and performance in objective tests. *Psychology Studies*, 33 (1), 151-159

Brodaty, H., & Donkin, M. (2009). Family caregivers of people with dementia. *Dialogues in Clinical Neuroscience*, 11(2), 217

Brunoni, A. R., Vanderhasselt, M. A., Boggio, P. S., Fregni, F., Dantas, E. M., Mill, J. G.,Burrows, C. J., & Muller, J. G. (1998). Oxidative nucleobase modifications leading to strand scission. *Chemical Reviews*, 98(3), 1109-1152

Cameron, I., Curran, S., Newton, P., Petty, D., & Wattis, J. (2000). Use of donepezil for the treatment of mild-moderate Alzheimer's disease: an audit of the assessment and treatment of patients in routine clinical practice. *International Journal of Geriatric Psychiatry*, 15(10), 887-891

Cameron, O. G. (2001). *Visceral sensory neuroscience: Interoception*. Oxford University Press

Cechetto, D. F. (1990). Role of the cerebral cortex in autonomic function. *Central Regulation of Autonomic Functions*, 208-223

Chen, C., & Zissimopoulos, J. M. (2018). Racial and ethnic differences in trends in dementia prevalence and risk factors in the United States. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 4, 510-520.

Cheng, Z., Powley, T. L., Schwaber, J. S., & Doyle III, F. J. (1997). Vagal afferent innervation of the atria of the rat heart reconstructed with confocal microscopy. *Journal of Comparative Neurology*, 381(1), 1-17

Christie, J. E., Shering, A., Ferguson, J., & Glen, A. I. M. (1981). Physostigmine and arecoline: effects of intravenous infusions in Alzheimer presenile dementia. *The British Journal of Psychiatry*, 138(1), 46-50

Chu, C. C., Tranel, D., & Damasio, A. R. (1994). Impaired autonomic responses to emotionally significant stimuli in Alzheimer's disease. In *Society of Neuroscience Abstracts*, Vol. 20, p. 1006

Collins, O., Dillon, S., Finucane, C., Lawlor, B., & Kenny, R. A. (2012). Parasympathetic autonomic dysfunction is common in mild cognitive impairment. *Neurobiology of Aging*, 33(10), 2324-2333

Cross, A. J., Crow, T. J., Johnson, J. A., Perry, E. K., Perry, R. H., Blessed, G., & Tomlinson, B. E. (1984). Studies on neurotransmitter receptor systems in neocortex and hippocampus in senile dementia of the Alzheimer-type. *Journal of the Neurological Sciences*, 64(2), 109-117

Cundiff, J. L. (2012). Is mainstream psychological research "womanless" and "raceless"? An updated analysis. *Sex Roles*, 67(3-4), 158-173

Davis, A. M., & Natelson, B. H. (1993). Brain-heart interactions. The neurocardiology of

arrhythmia and sudden cardiac death. *Texas Heart Institute Journal*, 20(3), 158

Di Rienzo M, Bertinieri G, Mancina G, et al. (1983) A new method for evaluating the baroreflex role by a joint pattern analysis of pulse interval and systolic blood pressure series. *Medicine Biology Engineering Computers*. 23:313

Di Rienzo, M., Parati, G., Castiglioni, P., Tordi, R., Mancina, G., & Pedotti, A. (2001). Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 280(3), R744-R751

Dilworth-Anderson, P., Hendrie, H. C., Manly, J. J., Khachaturian, A. S., & Fazio, S. (2008). Diagnosis and assessment of Alzheimer's disease in diverse populations. *Alzheimer's & Dementia: the journal of the Alzheimer's Association*, 4(4), 305- 309

Direção-Geral da Saúde. (2011). Abordagem terapêutica das alterações cognitivas: norma da DGS n.º 53/2011, de 27/12/2011

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J., ... & Meguro, K. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *The Lancet Neurology*, 6(8), 734-746

Ducla -Soares JL, Santos-Bento M, Laranjo S, et al. (2007) Wavelet analysis of autonomic outflow of normal subjects on head-up tilt, cold pressor test, Valsalva manoeuvre and deep breathing. *Experimental Physiology*. ;92:677

Ducla-Soares, J. L., Guerreiro, A. S., Póvoa, P., Alvares, E., Guerreiro, L., Carrilho, F, ... & Carvalho, M. (1993). Pure autonomic failure. *Acta Medica Portuguesa*, 6(11), 533-7

Eichler, T., Thyrian, J. R., Hertel, J., Wucherer, D., Michalowsky, B., Reiner, K., ... & Hoffmann, W. (2015). Subjective memory impairment: no suitable criteria for case- finding of dementia in primary care. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 1(2), 179-186

Hartlage, L. C. (2008). *Essentials of Neuropsychological Assessment: Treatment Planning for Rehabilitation*. Springer Publishing Company

Ellard-Gray, A., Jeffrey, N. K., Choubak, M., & Crann, S. E. (2015). Finding the hidden participant: Solutions for recruiting hidden, hard-to-reach, and vulnerable populations. *International Journal of Qualitative Methods*, 14(5)

Esiri, M. M., Pearson, R. C., Steele, J. E., Bowen, D. M., & Powell, T. P. (1990). A quantitative study of the neurofibrillary tangles and the choline acetyltransferase activity in the cerebral cortex and the amygdala in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 53(2), 161-165

Evans, H. H., & Evans, T. E. (1970). Methylation of the deoxyribonucleic acid of *Physarum polycephalum* at various periods during the mitotic cycle. *Journal of Biological Chemistry*, 245(23), 6436-6441

Evans, M., Ellis, A., Watson, D., & Chowdhury, T. (2000). Sustained cognitive improvement following treatment of Alzheimer's disease with donepezil. *International Journal of Geriatric Psychiatry*, 15(1), 50-53

Ferini-Strambi, L., & Smirne, S. (1997). Cardiac autonomic function during sleep in several neuropsychiatric disorders. *Journal of Neurology*, 244(1), S29-S36

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189-198

Freitas, S., Simões, M. R., Alves, L., & Santana, I. (2012). Montreal Cognitive Assessment: influence of sociodemographic and health variables. *Archives of Clinical Neuropsychology*, 27(2), 165-175

Friedland, R., Brun, A., & Budinger, T. (1985). Pathological and positron emission tomographic correlations in Alzheimer's disease. *Lancet (London, England)*, 1(8422), 228-228

Gallo, J. M., & Anderton, B. H. (1989). Ubiquitous variations in nerves. *Nature*, 337(6209), 687

Gillum, R. F., & Obisesan, T. O. (2011). Differences in mortality associated with dementia in US blacks and whites. *Journal of the American Geriatrics Society*, 59(10), 1823-1828

Ginó, S., Mendes, T., Ribeiro, F., Mendonça, A., Guerreiro, M., & Garcia, C. (2008). Escala de queixas de memória. *Grupo de Estudos de Envelhecimento Cerebral e Demências, editores. Escala e Testes na demência. Lisboa: GEECD*, 117-20

Golby, A., Silverberg, G., Race, E., Gabrieli, S., O'Shea, J., Knierim, K., ... & Gabrieli, J. (2005). Memory encoding in Alzheimer's disease: an fMRI study of explicit and implicit memory. *Brain*, 128(4), 773-787

Goldstein, D. S., Robertson, D., Esler, M., Straus, S. E., & Eisenhofer, G. (2002). Dysautonomias: clinical disorders of the autonomic nervous system. *Annals of Internal Medicine*, 137(9), 753-763

Gonçalves-Pereira, M., & Sampaio, D. (2011). Family psychoeducation in dementia: from clinic to public health. *Portuguese Journal of Public Health*, 29 (1), 3-10

Gottfries, C. G. (1990). Neurochemical aspects of dementia disorders. *Dementia and Geriatric Cognitive Disorders*, 1(1), 56-6

Guerreiro, M. P. S. A., Silva, A. P., Botelho, M. A., Leitão, O., Castro-Caldas, A., & Garcia, (1994). Adaptação à população portuguesa da tradução do Mini Mental State Examination (MMSE). *Revista Portuguesa de Neurologia*, 1(9), 9-10

Gurland, B. J. (1981). The borderlands of dementia: the influence of sociocultural characteristics on rates of dementia occurring in the senium. *Aging*, 15, 61-84

Gurland, B. J., Wilder, D. E., Lantigua, R., Stern, Y., Chen, J., Killeffer, E. H., & Mayeux, Hainsworth, R. (1995). The control and physiological importance of heart rate. *Heart rate variability*, 3-9

Haxby, J. V., Horwitz, B., Ungerleider, L. G., Maisog, J. M., Pietrini, P., & Grady, C. L. (1994). The functional organization of human extrastriate cortex: a PET-rCBF study of selective attention to faces and locations. *Journal of Neuroscience*, 14(11), 6336- 6353

Hayflick, L. (2000). The future of ageing. *Nature*, 408(6809), 267

Hirsch, J. A., & Bishop, B. (1981). Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. *American Journal of Physiology-Heart and Circulatory*

Hirsch, J. A., Bishop, B., & York, J. (1996). Role of parasympathetic (vagal) cardiac control in elevated heart rates of smokers. *Addiction Biology*, 1(4), 405-413

Hofman, A., Rocca, W. A., Brayne, C., Breteler, M. M. B., Clarke, M., Cooper, B., ... & Heeren, T. J. (1991). The prevalence of dementia in Europe: a collaborative study of 1980–1990 findings. *International Journal of Epidemiology*, 20(3), 736-748

Huppert, F. A., Brayne, C., & O'Connor, D. W. (Eds.). (1994). *Dementia and Normal Aging*. Cambridge University Press

Iacoviello, M., Guida, P., Forleo, C., Sorrentino, S., D'Alonzo, L., & Favale, S. (2008). Impaired arterial baroreflex function before nitrate-induced vasovagal syncope during head-up tilt test. *Europace*, 10(10), 1170-1175

Iliffe, S., & Manthorpe, J. (2004). The debate on ethnicity and dementia: from category fallacy to person-centered care?. *Aging & Mental Health*, 8(4), 283-292

INE, I. (2009). Projeções de população residente em Portugal 2008-2060. *Destaque, Lisboa-Portugal*

Kaufmann, H., & Biaggioni, I. (2003). Autonomic failure in neurodegenerative disorders. In *Seminars in Neurology*, Vol. 23, 04, pp. 351-364 Thieme Medical Publishers, Inc.

Kaye, W. H., Sitaram, N., Weingartner, H., Ebert, M. H., Smallberg, S., & Gillin, J. C. (1982). Modest facilitation of memory in dementia with combined lecithin and anticholinesterase treatment. *Biological Psychiatry*

Kerr, W. C., & Stockwell, T. (2012). Understanding standard drinks and drinking guidelines. *Drug and Alcohol Review*, 31(2), 200-205

Kneebone, I. I., & Martin, P. R. (2003). Coping and caregivers of people with dementia. *British Journal of Health Psychology*, 8(1), 1-17

Kolb, B., & Whishaw, I. Q. (2009). *Fundamentals of human neuropsychology*. Macmillan;

Kukanova, B., & Mravec, B. (2006). Complex intracardiac nervous system. *Bratislavske*

lekarske listy, 107(3), 45;

Laborde, S., Furley, P., & Schempp, C. (2015). The relationship between working memory, reinvestment, and heart rate variability. *Physiology & Behavior*, 139, 430- 436

Lane, C. A., Barnes, J., Nicholas, J. M., Sudre, C. H., Cash, D. M., Parker, T. D., ... & Murray-Smith, H. (2019). Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *The Lancet Neurology*

Lane, R. D., Reiman, E. M., Ahern, G. L., & Thayer, J. F. (2001). 21. Activity in medial prefrontal cortex correlates with vagal component of heart rate variability during emotion. *Brain and Cognition*, 47(1-2), 97-100

Lehrer, P. M., Karavidas, M. K., Lu, S. E., Feldman, J., Kranitz, L., Abraham, S., ... & Reynolds, R. (2008). Psychological treatment of comorbid asthma and panic disorder: a pilot study. *Journal of anxiety disorders*, 22(4), 671-683

Lehrer, P. M., Vaschillo, E., Vaschillo, B., Lu, S. E., Eckberg, D. L., Edelberg, R., ... & Hamer, R. M. (2003). Heart rate variability biofeedback increases baroreflex gain and peak expiratory flow. *Psychosomatic Medicine*, 65(5), 796-805

Low PA, Benarroch EE. In: Low PA, Benarroch EE, editors. Clinical autonomic disorders. 3rd ed. Philadelphia, PA/London: Lippincott Williams & Wilkins; 2008

Lowin, A., Knapp, M., & McCrone, P. (2001). Alzheimer's disease in the UK: comparative evidence on cost of illness and volume of health services research funding. *International Journal of Geriatric Psychiatry*, 16(12), 1143-1148

Mann, D. M., Yates, P. O., & Hawkes, J. (1982). The noradrenergic system in Alzheimer and multi-infarct dementias. *Journal of Neurology, Neurosurgery & Psychiatry*, 45(2), 113-119

Marieb, E. N., & Hoehn, K. (2007). *Human Anatomy & Physiology*. Pearson Education

Mateo, J., Torres, A., & Rieta, J. J. (2011). An efficient method for ectopic beats cancellation based on radial basis function. In *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 6947-6950

Mathias CJ, Bannister R. Autonomic failure: a textbook of clinical disorders of the autonomic nervous system. 5th ed. Oxford University Press; 2012

Mathias, C. J. (1999). Separating the primary autonomic failure syndromes, multiple system atrophy, and pure autonomic failure from Parkinson's disease. *Advances in Neurology*, 80, 353-361

McCraty, R., & Childre, D. (2010). Coherence: bridging personal, social, and global health. *Alternatives to Therapeutic Health Medicine*, 16(4), 10-24

McCraty, R., Atkinson, M., & Bradley, R. T. (2004). Electrophysiological evidence of intuition: Part 1. The surprising role of the heart. *The Journal of Alternative & Complementary Medicine*, 10(1), 133-143

McCraty, R., Atkinson, M., & Tomasino, D. (2003). Impact of a workplace stress reduction program on blood pressure and emotional health in hypertensive employees. *The Journal of Alternative & Complementary Medicine*, 9(3), 355-369

McCraty, R., Atkinson, M., Tomasino, D., & Bradley, R. T. (2009). The Coherent Heart Heart-Brain Interactions, Psychophysiological Coherence, and the Emergence of System-Wide Order. *Integral Review: A Transdisciplinary & Transcultural Journal for New Thought, Research, & Praxis*, 5(2)

McKeith, I. G. (2006). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. *Journal of Alzheimer's Disease*, 9(s3), 417-423

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34(7), 939-939

McNamee, P., Bond, J., & Buck, D. (2001). Costs of dementia in England and Wales in the 21st century. *The British Journal of Psychiatry*, 179(3), 261-266

Mitchell, A. J. (2008). The clinical significance of subjective memory complaints in the

diagnosis of mild cognitive impairment and dementia: a meta-analysis. *International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences*, 23(11), 1191-1202

Morgado, J., Rocha, C. S., Maruta, C., Guerreiro, M., & Martins, I. P. (2009). Novos valores normativos do mini-mental state examination. *Sinapse*, 9(2), 10-16

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*

Mukadam, N., Cooper, C., & Livingston, G. (2011). A systematic review of ethnicity and pathways to care in dementia. *International Journal of Geriatric Psychiatry*, 26(1), 12-20

Müller-Hill, B., & Beyreuther, K. (1989). Molecular biology of Alzheimer's disease. *Annual Review of Biochemistry*, 58(1), 287-307

Miyamoto T, MM, SK, NM, IM HK, Miyamoto T, Miyamoto M, Suzuki K, Nishibayashi M, Iwanami M, Hirata K, Miyamoto T, Miyamoto M, Suzuki K, Nishibayashi M, Iwanami M, Hirata K (2008). 123I-MIBG cardiac scintigraphy provides clues to the underlying neurodegenerative disorder in idiopathic REM. *Sleep* 31, 717-723.

Napadow, V., Dhond, R., Conti, G., Makris, N., Brown, E. N., & Barbieri, R. (2008). Brain correlates of autonomic modulation: combining heart rate variability with fMRI. *Neuroimage*, 42(1), 169-177

Neafsey, E. J. (1991). Prefrontal cortical control of the autonomic nervous system: anatomical and physiological observations. In *Progress in brain research*, Vol. 85, 147-166, Elsevier

Neary, D., Snowden, J. S., Gustafson, L., Passant, U., Stuss, D., Black, S. A. S. A., ... & Boone, K. (1998). Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*, 51(6), 1546-1554

Neto, E. S., Custaud, M. A., Cejka, J. C., Abry, P., Frutoso, J., Gharib, C., & Flandrin, P. (2004). Assessment of cardiovascular autonomic control by the empirical mode decomposition. *Methods of Information in Medicine*, 43(01), 60-65

Nielsen, T. R., Vogel, A., Phung, T. K. T., Gade, A., & Waldemar, G. (2011). Over-and under-

diagnosis of dementia in ethnic minorities: a nationwide register-based study. *International Journal of Geriatric Psychiatry*, 26(11), 1128-1135

Nielsen, T. R., Vogel, A., Riepe, M. W., de Mendonça, A., Rodriguez, G., Nobili, F., ... & Waldemar, G. (2011). Assessment of dementia in ethnic minority patients in Europe: a European Alzheimer's Disease Consortium survey. *International Psychogeriatrics*, 23(1), 86-95

Nitrini, R., Caramelli, P., Bottino, C. M. C., Damasceno, B. P., Brucki, S. M. D., & Anghinah, R. (2005). Diagnóstico de doença de Alzheimer no Brasil: critérios diagnósticos e exames complementares. *Archives Neuropsychiatry*, 63(3-A), 713-719

Nunes, T. F. G. (2017). Communication strategies of third sector organizations: Alzheimer's disease and other dementias in Portugal

O'Bryant, S. E., Waring, S. C., Cullum, C. M., Hall, J., Lacritz, L., Massman, P. J., ... & Doody, R. (2008). Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas

Alzheimer's research consortium study. *Archives of Neurology*, 65(8), 1091-1095

Oppenheimer, S. M., Gelb, A., Girvin, J. P., & Hachinski, V. C. (1992). Cardiovascular effects of human insular cortex stimulation. *Neurology*, 42(9), 1727-1727

Pannain, G. D., Ribeiro, C. C., Jacob, M. B., Pires, L. A., & Almeida, A. L. M. (2019). Relato de experiência: Dia Mundial do Acidente Vascular Cerebral. *HU Revista*, 45(1), 104-108

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease: A critical review. *Brain*, 122(3), 383-404

Pinquart, M., & Sörensen, S. (2005). Ethnic differences in stressors, resources, and psychological outcomes of family caregiving: A meta-analysis. *The Gerontologist*, 45(1), 90-106

Podewils, L. J., Guallar, E., Kuller, L. H., Fried, L. P., Lopez, O. L., Carlson, M., & Lyketsos, C. G. (2005). Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *American Journal of Epidemiology*, 161(7), 639-651

Potter, G. G., Plassman, B. L., Burke, J. R., Kabeto, M. U., Langa, K. M., Llewellyn, D. J., R. (1991). Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, 30(4), 572-580;

Gurland, B. J., Wilder, D. E., Lantigua, R., Stern, Y., Chen, J., Killeffer, E. H., & Mayeux, R. (1999). Rates of dementia in three ethnoracial groups. *International Journal of Geriatric Psychiatry*, 14(6), 481-493

Reisberg, B., Doody, R., Stöffler, A., Schmitt, F., Ferris, S., & Möbius, H. J. (2003). Memantine in moderate-to-severe Alzheimer's disease. *New England Journal of Medicine*, 348(14), 1333-1341

Rémy, F., Mirrashed, F., Campbell, B., & Richter, W. (2005). Verbal episodic memory impairment in Alzheimer's disease: a combined structural and functional MRI study. *Neuroimage*, 25(1), 253-266

Pagani M, Lombardi F, Guzzetti S, et al.(1986) Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circulation Research*. 59:178

Roman GC, Tatemichi TK, Erkinjuntti T. et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43(2):250-60

Ruano, L., Araújo, N., Branco, M., Barreto, R., Moreira, S., Pais, R., ... & Barros, H. (2019). Prevalence and Causes of Cognitive Impairment and Dementia in a Population-Based Cohort from Northern Portugal. *American Journal of Alzheimer's Disease & Other Dementias*, 34(1), 49-56

Santana, I., Farinha, F., Freitas, S., Rodrigues, V., & Carvalho, Á. (2015). Epidemiologia da Demência e da Doença de Alzheimer em Portugal: Estimativas da Prevalência e dos Encargos Financeiros com a Medicação. *Acta Médica Portuguesa*, 28(2), 182- 188

Santana, I., Hard, D., Lemos, R., Costa, V., Pereira, M., Simões, M. R., & Freitas, S. (2016). Mini-Mental State Examination: Evaluation of New Normative Data in Cognitive Deficit Screening

and Diagnosis. Portuguese Medical Record, 29 (4)

Schenk, D., Barbour, R., Dunn, W., Gordon, G., Grajeda, H., Guido, T., ... & Kholodenko, Schmand, B., Jonker, C., Hooijer, C., & Lindeboom, J. (1996). Subjective memory complaints may announce dementia. *Neurology*, 46(1), 121-125

Shaffer, F., & Venner, J. (2013). Heart rate variability anatomy and physiology. *Bio-feedback*, 41(1), 13-25

Shaghaghi, A., Bhopal, R. S., & Sheikh, A. (2011). Approaches to recruiting 'hard-to-reach' populations into research: a review of the literature. *Health promotion perspectives*, 1(2), 86

Sinden, J. D., Hodges, H., & Gray, J. A. (1995). Neural transplantation and recovery of cognitive function. *Behavioral and Brain Sciences*, 18(1), 10-35

Sink, K. M., Covinsky, K. E., Newcomer, R., & Yaffe, K. (2004). Ethnic differences in the prevalence and pattern of dementia-related behaviors. *Journal of the American Geriatrics Society*, 52(8), 1277-1283

Sousa, M., Pereira, A., Costa, R., & Gomes, P. (2017). Subjective Memory Complaints in Primary Health Care: A Study Follow up. *Psychology, Community & Health*, 6 (1), 63

Sydor, A. (2013). Conducting research into hidden or hard-to-reach populations. *Nurse Researcher*, 20(3)

Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J*. 1996;17:354.

Tavares, C., Laranjo, S., Santos, M., & Rocha, I. (2010). An instantaneous time-frequency methodology applied to evaluation of blood pressure changes during HUT of multiple system atrophy patients. *Clinical Autonomic Research*, 20, 150-151

Tavares, C., Martins, R. C., Laranjo, S., & Rocha, I. (2011, March). Computational tools for assessing cardiovascular variability. In *1st Portuguese Biomedical Engineering Meeting*, 1-6

Thal, L. J. (1992). Cholinomimetic therapy in Alzheimer's disease. Thayer, J. F., & Sternberg, E. (2006). Beyond heart rate variability: vagal regulation of allostatic systems. *Annals of the New York Academy of Sciences*, 1088(1), 361-372

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Annals of Behavioral Medicine*, 37(2), 141-153

Tractenberg, R. E., Schafer, K., & Morris, J. C. (2001). Interobserver disagreements on clinical dementia rating assessment: interpretation and implications for training. *Alzheimer Disease & Associated Disorders*, 15(3), 155-161

Tuerk, R., & Sauer, J. (2015). Dementia in a Black and minority ethnic population: characteristics of presentation to an inner London memory service. *BJPsych Bulletin*, 39(4), 162-166

V. L., & Kaye, J. (2007). Validity of the clinical dementia rating scale for the detection and staging of dementia in Brazilian patients. *Alzheimer Disease & Associated Disorders*, 21(3), 210-217

Verkerk, A. O., Remme, C. A., Schumacher, C. A., Scicluna, B. P., Wolswinkel, R., de Jonge, B., ... & Veldkamp, M. W. (2012). Functional Nav1. 8 channels in intracardiac neurons: the link between SCN10A and cardiac electrophysiology. *Circulation Research*, 111(3), 333-343

Vitiello, B., Veith, R. C., Molchan, S. E., Martinez, R. A., Lawlor, B. A., Radcliffe, J., ... & Sunderland, T. (1993). Autonomic dysfunction in patients with dementia of the Alzheimer type. *Biological Psychiatry*, 34(7), 428-433

Wang, S. *et al.* (1994). Cardiovascular autonomic functions in Alzheimer's disease. *Age and Ageing*, 23(5), 400-404

Wilcock, G. K., Esiri, M. M., Bowen, D. M., & Hughes, A. O. (1988). The differential involvement

of subcortical nuclei in senile dementia of Alzheimer's type. *Journal of Neurology, Neurosurgery & Psychiatry*, 51(6), 842-849

Winblad, B., Amouyel, P., Andrieu, S., Ballard, C., Brayne, C., Brodaty, H., ... & Fratiglioni, L. (2016). Defeating Alzheimer's disease and other dementias: a priority for European science and society. *The Lancet Neurology*, 15(5), 455-532

Woods, B., Aguirre, E., Spector, A. E., & Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database of Systematic Reviews*, 2

Wu, Y. T., Fratiglioni, L., Matthews, F. E., Lobo, A., Breteler, M. M., Skoog, I., & Brayne, Wykle, M., & Segal, M. (1991). A comparison of black and white family caregivers experience with dementia. *Journal of National Black Nurses' Association: JNBNA*, 5(1), 29-41

Xavier R, Laranjo S, Ducla-Soares E, et al. The Valsalva maneuver revisited by wavelets. *Revista Portuguesa de Cardiologia*. 2008;27: 435-41

Xu, J., Zhang, Y., Qiu, C., & Cheng, F. (2017). Global and regional economic costs of dementia: a systematic review. *The Lancet*, 390, S47

Youn, J. C., Kim, K. W., Lee, D. Y., Jhoo, J. H., Lee, S. B., Park, J. H., ... & Woo, J. I. (2009). Development of the subjective memory complaints questionnaire. *Dementia and Geriatric Cognitive Disorders*, 27(4), 310-317

Zulli R, Nicosia F, Borroni B, Agosti C, Prometti P, et al. (2005) QT dispersion and heart rate variability abnormalities in Alzheimer's disease and in mild cognitive impairment. *Journal American Geriatric Society* 53: 2135-2139.

8. ATTACHMENTS

ATTACHMENT (8.a)



CONSENTIMENTO INFORMADO – folha de informação ao doente

Por favor, leia com atenção o presente documento. Se achar que algo está incorrecto ou que não está claro, não hesite em solicitar mais informações. Se concorda com a proposta que lhe foi feita, queira assinar o documento no seu final e rubricar a primeira página. Este documento tem 6 páginas.

A relação investigadora - voluntário participante em projectos de investigação científica é baseada na confiança mútua.

A Faculdade de Medicina de Lisboa (FMUL), o Centro Cardiovascular Universitário de Lisboa (CCUL) e o Hospital Prof. Dr. Fernando da Fonseca (HFF) dispõem de procedimentos que permitem salvaguardar os direitos de ambos.

O investigador obriga-se a informar o voluntário participante sobre a natureza da sua participação no projecto, potenciais vantagens e inconvenientes, podendo o mesmo aceitar participar ou não aceitar participar no projecto proposto.

Este estudo tem carácter voluntário sendo possível ao participante poder-se retirar em qualquer altura, não sendo novos dados adicionados ao estudo e sem que seja prejudicado o seu acompanhamento clínico.

=====

Título do estudo: A Avaliação da função autonómica numa população de doentes afro-descendentes com demência ligeira - Um estudo piloto.

Promotor do estudo (entidade responsável pela execução do projecto): Centro Cardiovascular da Universidade de Lisboa - Faculdade de Medicina da Universidade de Lisboa.

Co-Promotor: Hospital Prof. Dr. Fernando da Fonseca (Serviço de Neurologia).

Tipo de estudo: Projecto de investigação, prospectivo, realizado em regime de ambulatório.

Objectivo do projecto: Avaliar a Função Autonómica em Doentes Afro-descendentes de Raça Negra com Demência Ligeira, por metodologias não invasivas, de uma população de doentes pertencente aos concelhos de Amadora e de Sintra.

Enquadramento do estudo:

Informação com diversas origens é consensual a indicar que o número de pessoas com demência, de diferentes etiologias, está a aumentar devido ao envelhecimento da população e à melhoria das metodologias diagnósticas. A demência em si não discrimina entre etnias, no entanto, não existem em Portugal estudos de base populacional sobre a prevalência e as características de demência numa raça ou etnia específica. Por outro lado, os mecanismos subjacentes ao envelhecimento parecem estar mais pronunciados em doentes com demência à qual se tem, também, associado, disfunção nas estruturas cerebrais que coordenam funções viscerais. Algumas destas estruturas pertencem à rede autonómica central. No entanto, a relação entre disautonomia e demência não está ainda bem definida para cada etnia. Assim, no âmbito deste estudo piloto, pretendemos investigar a função autonómica em doentes negros com demência ligeira diagnosticada clinicamente, de ambos os sexos e idade ≥ 50 anos. Após anamnese, história clínica, exame físico e neuropsicológico, a função autonómica será avaliada por metodologias no domínio do tempo e no tempo-escala aplicadas às variáveis fisiológicas recolhidas durante a *Respiração Profunda*; *Manobra de Valsava* e *Contração Isotónica*. Assim, espera-se com este estudo entender melhor a disfunção autonómica subjacente à demência ligeira em doentes de raça negra comparativamente a um grupo de controlo; distinguir diferentes mecanismos de progressão da doença entre raça caucasiana e raça negra de uma população portuguesa de doentes; contribuir para a caracterização epidemiológica desta população; contribuir para a procura de terapêuticas específicas e melhorar o apoio a estes doentes, às suas famílias e cuidadores.

Duração do Estudo (recolha de dados/amostra): Início em Fevereiro de 2018 por um período previsto de 2 (dois) anos.

Investigador principal pelo projecto: Isabel Rocha, Professora Universitária-Associada c/Agregação da Faculdade de Medicina de Lisboa; Investigadora Principal no CCUL.

Investigador responsável pelo projecto no Hospital Prof. Doutor Fernando da Fonseca (HFF): Ana Valverde, Assistente Graduada de Neurologia (HFF); Investigadora Principal no Centro de Ensaios Clínicos de Neurologia (HFF).

Co-Investigador no HFF e Aluno da FMUL: André Carvalho, Assistente de Neuropsicologia (Serviço MFR); Sub-investigador no Centro de Ensaios Clínicos de Neurologia (HFF) e Aluno de Neurociências (FMUL) associado ao grupo de Funções Autonómicas Cardiovasculares do CCUL.

Investigador responsável pelo projecto na Faculdade de Ciências da Universidade de Lisboa (FCUL): Hugo Ferreira, Professor Universitário-Auxiliar na FCUL e Investigador Principal no IBEB (Instituto de Biofísica e Engenharia Biomédica).

Protocolo

Procedimentos principais:

- 1) Selecção dos doentes (população-alvo) a avaliar:
 - 1.1 idade ≥ 50 anos de ambos os sexos, com registo de *anos de escolaridade; naturalidade; história familiar de demência; dependência de substâncias; hipertensão e dislipidemia*.
 - 1.2 diagnóstico clínico de demência em fase ligeira baseado no DSM-IV-R (Manual Diagnóstico e Estatístico de Transtornos Mentais da Associação Americana de Psiquiatria).
 - 1.3 exclusão de doentes que apresentem: diabetes com mau controlo metabólico e/ou insulino-tratados; doença pulmonar obstrutiva crónica; hipotensão ortostática; síncope reflexa; arritmias cardíacas e fibrilhação auricular medicados com beta-bloqueantes; insuficiência cardíaca moderada a grave; cirurgias cardíacas ou implantes cardíacas; medicação bloqueadora beta-adrenérgica ou outras demências secundárias a condições orgânicas (ex.: hipotiroidismo, hematoma subdural crónico; asma; esclerose múltipla).
- 2) Registo pelo processo clínico, quando presente, de valores dos hemogramas de rotina com os seguintes doseamentos: HIV; VDRL; Vitamina B12; Ácido Fólico e níveis hormonais da tiróide.
- 3) Registo pelo processo clínico, quando presente, da volumetria dos Hipocampus suportado por técnicas de neuroimagem: TAC-CE ou RM-CE.
- 4) Aplicação de Medidas Neuropsicológicas para confirmação de Diagnóstico de Demência Ligeira, baseadas nos seguintes instrumentos:
 - 3.1 **MMSE** (Exame Breve do Estado Mental, com valores normativos referentes a população portuguesa): prova de papel e lápis; duração (aproximada): **10 minutos**.
 - 3.2 **CDR** (Avaliação Clínica da Demência, com valores normativos referentes a população portuguesa): entrevista semi-estruturada com cuidador e doente; duração (aproximada) **30/40 minutos**.
 - 3.3 **QSM** (Escala de Queixas Subjectivas de Memória, com valores normativos referentes a população portuguesa): questionário de auto-avaliação com 10 questões de aproximadamente: **5 minutos**.
- 5) Medição de variáveis cardiovasculares: frequência cardíaca e pressão arterial. A medição da frequência cardíaca e da pressão arterial é não invasiva e indolor, ou seja, é feita sem utilização de qualquer instrumento que entre na pele e/ou provoque dor. Para isso serão colocados, quatro eléctrodos no peito, um sensor no dedo anelar da mão direita e uma braçadeira no braço esquerdo. Os sinais registados são enviados para um computador para serem analisados.

6) **Avaliação Autonómica: 20/30 minutos.**

Permite saber como está o estado do sistema nervoso que controla a função de todos os órgãos (coração, pulmões, rins, etc). É constituída, neste caso, por três procedimentos: **1.º respiração profunda** em que se vai respirando mais lentamente a um ritmo específico durante 1 minuto; **2.º manobra de Valsalva** em que se sopra para um tubo com um certo valor de pressão durante 15s; e **3.º contração isométrica** em que se faz força com a mão dominante num dinamómetro sem o largar, com um certo valor de pressão, durante 5 minutos.

Durante estes procedimentos, a pessoa estará sentada numa cadeira, calma e tranquila, não podendo beber café, tomar chá ou fumar nas 12 horas anteriores ao exame. Durante os procedimentos será medida a pressão arterial e a frequência cardíaca. Estes procedimentos não são invasivos e são indolores, ou seja, são feitos sem utilização de qualquer instrumento que entre na pele e/ou povoque dor.

=====

INFORMAÇÃO COMPLEMENTAR

Devido à natureza não invasiva do estudo *não se esperam* inconvenientes para o participante.

É assegurada a assistência durante o tempo de monitorização, bem como é garantido o livre acesso a todas as informações e esclarecimentos adicionais sobre o estudo.

A equipa de investigação está sujeita a sigilo e confidencialidade. Ou seja, cada participante tem um código de identificação que não deixa que o seu nome e/ou identidade seja conhecido.

Os resultados das medições serão apenas usados para fins científicos. Não resultarão do estudo para cada investigador e/ou instituições envolvidas outros benefícios que não os de carácter científico. Ou seja, nenhum dos técnicos ou investigadores recebe qualquer dinheiro extra por efectuar este estudo.

Contactos de E-mail dos Investigadores:

- **Dr. André Carvalho** (co-responsável no HFF)
amc.psicologia@gmail.com
Unidade de Neuropsicologia - Hospital Prof. Dr. Fernando da Fonseca E.P.E . IC 19, 2720-276 Amadora, Portugal.

- **Prof.ª Ana Valverde** (responsável no HFF)
ahvalverde82@gmail.com
Serviço de Neurologia - Hospital Prof. Dr. Fernando da Fonseca E.P.E . IC 19, 2720-276 Amadora, Portugal.

- **Prof.º Hugo Ferreira** (responsável na FCUL/IBEB)
hatdferreira@gmail.com
Instituto de Biofísica e Engenharia Biomédica - Faculdade de Ciências da Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal.

- **Prof.ª Isabel Rocha** (responsável pelo estudo / CCUL-FMUL)
isabelrocha0@gmail.com
Instituto de Fisiologia, Faculdade de Medicina da Universidade de Lisboa, Av. Prof Egas Moniz, 1649-028 Lisboa, Portugal.

Se concorda com a proposta que lhe foi feita, queira assinar este documento a seguir.



CONSENTIMENTO INFORMADO

Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas. Aceito participar de livre vontade no projecto acima mencionado. Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Data: ____ / ____ / ____

Nome do participante (maiúsculas) _____

Assinatura do participante: _____

Confirmo que expliquei ao participante, de forma adequada e inteligível, os procedimentos, assim como os potenciais inconvenientes, e que entreguei o folheto de informação complementar.

Nome do investigador (maiúsculas) _____

Assinatura do investigador: _____

ATTACHEMENT (8.b)

Questionário de Avaliação Clínica da Demência

Esta é uma entrevista semi-estruturada. Coloque todas as perguntas que se seguem. Coloque quaisquer outras perguntas necessárias para determinar a CDR (Avaliação Clínica da Demência) do doente. Anote as informações das perguntas adicionais.

Perguntas sobre a memória para o informante (pessoa próxima do doente):

1. O doente tem problemas de memória ou raciocínio? ☐ Sim ☐ Não
- 1a. Se respondeu sim, o problema é constante (no sentido oposto de inconstante)? ☐ Sim ☐ Não
2. O doente consegue lembrar-se de acontecimentos recentes? ☐ Geralmente ☐ Às vezes ☐ Raramente
3. O doente consegue memorizar uma pequena lista de coisas (compras)? ☐ Geralmente ☐ Às vezes ☐ Raramente
4. Verificou-se algum declínio na memória ao longo do último ano? ☐ Sim ☐ Não
5. A memória do doente apresenta limitações ao ponto destas poderem ter interferido com as suas actividades do dia-a-dia há alguns anos (ou durante a sua vida activa)? (opinião de pessoas próximas do doente) ☐ Sim ☐ Não
6. O doente esquece-se completamente de um acontecimento importante (por exemplo, viagem, festa, casamento de família) a algumas semanas do acontecimento? ☐ Geralmente ☐ Às vezes ☐ Raramente
7. O doente esquece-se de pormenores marcantes desse acontecimento importante? ☐ Geralmente ☐ Às vezes ☐ Raramente
8. O doente esquece-se completamente de informações importantes do passado distante (por exemplo, data de nascimento, data de casamento, local de emprego)? ☐ Geralmente ☐ Às vezes ☐ Raramente
9. Fale-me de um acontecimento recente na vida do doente do qual ele se deveria lembrar. (Obtenha pormenores tais como o local do acontecimento, hora, convidados, duração, quando acabou e como o doente ou outros convidados chegaram lá, para posterior comparação com as respostas do doente).

No espaço de 1 semana: _____

No espaço de 1 mês: _____

10. Quando é que o doente nasceu? _____

11. Onde é que o doente nasceu? _____

12. Qual foi a última escola que o doente frequentou? _____

Nome _____

Cidade _____

Classe _____

13. Qual foi a ocupação/emprego principal do doente (ou emprego do parceiro, caso o doente não tivesse emprego)? _____

14. Qual foi o último emprego principal do doente (ou emprego do parceiro, caso o doente não tivesse emprego)? _____

15. Quando se reformou o doente (ou o parceiro) e porquê? _____

Questionário de Avaliação Clínica da Demência

Perguntas sobre a orientação para o informante:

Com que frequência sabe o doente exactamente:

1. O dia do mês?

☐ Geralmente ☐ Às vezes ☐ Raramente ☐ Não sei

2. O mês?

☐ Geralmente ☐ Às vezes ☐ Raramente ☐ Não sei

3. O ano?

☐ Geralmente ☐ Às vezes ☐ Raramente ☐ Não sei

4. O dia da semana?

☐ Geralmente ☐ Às vezes ☐ Raramente ☐ Não sei

5. O doente tem dificuldades de orientação em relação ao tempo (situar os acontecimentos no tempo)?

☐ Geralmente ☐ Às vezes ☐ Raramente ☐ Não sei

6. O doente consegue orientar-se em ruas que lhe são familiares?

☐ Geralmente ☐ Às vezes ☐ Raramente ☐ Não sei

7. Com que frequência sabe ele/ela como deslocar-se de um local para o outro, fora da sua área de residência?

☐ Geralmente ☐ Às vezes ☐ Raramente ☐ Não sei

8. Com que frequência consegue o doente orientar-se dentro de casa?

☐ Geralmente ☐ Às vezes ☐ Raramente ☐ Não sei

Questionário de Avaliação Clínica da Demência

Perguntas sobre o discernimento e resolução de problemas para o informante:

1. De um modo geral, se tivesse de avaliar a capacidade do doente para resolver problemas presentemente, consideraria essa capacidade:

☐ Tão boa como no passado
☐ Boa, mas não tanto como no passado
☐ Razoável
☐ Má
☐ Inexistente
2. Avalie a capacidade do doente para lidar com pequenas quantias de dinheiro (por exemplo, calcular trocos, deixar uma pequena gorjeta):

☐ Nenhuma perda de capacidade
☐ Alguma perda de capacidade
☐ Grave perda de capacidade
3. Avalie a capacidade do doente para lidar com assuntos financeiros ou comerciais complicados (por exemplo, verificar o livro de cheques, pagar contas):

☐ Nenhuma perda de capacidade
☐ Alguma perda de capacidade
☐ Grave perda de capacidade
4. O doente consegue lidar com uma pequena emergência doméstica (por exemplo, fuga de água nas canalizações, pequeno incêndio)?

☐ Tão bem como antes
☐ Pior do que antes, devido às dificuldades de raciocínio
☐ Pior do que antes, outra razão (porquê) _____

5. O doente consegue compreender situações ou explicações?

☐ Geralmente ☐ Às vezes ☐ Raramente ☐ Não sei
6. O doente comporta-se* de forma adequada [isto é, no seu estado habitual (pré-mórbido)] em situações sociais e interações com outras pessoas?

☐ Geralmente ☐ Às vezes ☐ Raramente ☐ Não sei

*Esta pergunta avalia o comportamento, não a aparência.

Questionário de Avaliação Clínica da Demência

Perguntas sobre o relacionamento com a comunidade para o informante:

Trabalho

1. O doente ainda trabalha? ☐ Sim ☐ Não ☐ N/A
Se não for aplicável, prossiga para a pergunta 4
Se respondeu Sim, prossiga para a pergunta 3
Se respondeu Não, prossiga para a pergunta 2
2. Os problemas de memória ou raciocínio contribuíram para a decisão do doente em se reformar? (A pergunta 4 é a seguinte) ☐ Sim ☐ Não ☐ N/S
3. O doente tem dificuldades significativas no emprego, devido aos problemas de memória ou raciocínio?
☐ Raramente ou nunca ☐ Às vezes ☐ Geralmente ☐ Não sei

Vida social

4. O doente já alguma vez conduziu? ☐ Sim ☐ Não
O doente conduz actualmente? ☐ Sim ☐ Não
Se respondeu Não, é devido aos problemas de memória ou raciocínio? ☐ Sim ☐ Não
5. Se o doente ainda conduz, verificam-se problemas ou riscos devido a um raciocínio insuficiente? ☐ Sim ☐ Não
- *6. O doente consegue fazer compras sozinho?
☐ Raramente ou nunca (Tem de ser acompanhado em qualquer ida às compras) ☐ Às vezes (Compra apenas um número limitado de coisas; compra coisas a dobrar ou esquece-se de coisas necessárias) ☐ Geralmente ☐ Não sei
7. O doente consegue realizar actividades fora de casa sozinho?
☐ Raramente ou nunca (De um modo geral não é capaz de realizar actividades sem ajuda) ☐ Às vezes (Participação limitada e/ou rotineira, por exemplo, participação superficial em actividades religiosas ou reuniões; idas ao cabeleireiro) ☐ Geralmente (Participação activa em actividades, por exemplo, votações) ☐ Não sei
8. O doente envolveu-se em funções sociais fora de casa? ☐ Sim ☐ Não
Se respondeu Não, porque não? _____
9. Avaliando o comportamento do doente, um observador casual diria que o doente está doente? ☐ Sim ☐ Não
10. Caso se encontre num lar de terceira idade, o doente participa activamente em funções sociais (raciocínio)? ☐ Sim ☐ Não

IMPORTANTE:

Existem informações suficientes para avaliar o nível de limitação do doente nas actividades em comunidade?

Se respondeu Não, tente obter mais informações

Relacionamento com a comunidade: Tais como actividades religiosas, visitas a amigos ou familiares, actividades políticas, organizações profissionais, como a associação de advogados, outros grupos profissionais, clubes, organizações de serviços, programas educativos.

***Se for necessário, acrescente notas para esclarecer o nível de funcionamento do doente nesta área.**

Questionário de Avaliação Clínica da Demência

Perguntas sobre as actividades domésticas e passatempos para o informante:

1a. Que alterações ocorreram na capacidade do doente em realizar tarefas domésticas? _____

1b. Quais são as tarefas que o doente ainda faz bem? _____

2a. Quais são as alterações verificadas na capacidade do doente em realizar passatempos? _____

2b. Quais são os passatempos que o doente ainda realiza bem? _____

3. Caso se encontre num lar de terceira idade, quais são as actividades que o doente já não faz bem (tarefas domésticas e passatempos)? _____

Actividades do dia-a-dia (The Dementia Scale of Blessed):

	Nenhuma perda de capacidade		Grave perda de capacidade
4. Capacidade de desempenhar tarefas domésticas	0	0,5	1

Descreva: _____

5. O doente tem capacidade para realizar tarefas ao nível de:
(Selecione uma resposta. Não é necessário perguntar directamente ao informante).

- ☐ Nenhum funcionamento significativo.
(Realiza actividades simples, como fazer a cama, apenas com muita supervisão)
- ☐ Funciona apenas em actividades limitadas.
(Com alguma supervisão, lava a loiça com uma eficiência aceitável; põe a mesa)
- ☐ Funciona de forma independente em algumas actividades.
(Utiliza aparelhos, como um aspirador; prepara refeições simples)
- ☐ Funciona em actividades habituais, mas não ao nível habitual.
- ☐ Funciona normalmente em actividades habituais.

IMPORTANTE:

Existem informações suficientes para avaliar o nível de limitação do doente nas actividades domésticas e passatempos?

Se respondeu Não, tente obter mais informações.

Tarefas Domésticas: Como cozinhar, tratar da roupa, limpar, fazer compras, levar o lixo à rua, trabalhar no quintal, realizar tarefas simples de manutenção e reparações domésticas básicas.

Passatempos: Costura, pintura, trabalhos manuais, leitura, entretenimento, fotografia, jardinagem, assistir a peças de teatro ou sinfonias, carpintaria, prática de desporto.

Questionário de Avaliação Clínica da Demência

Perguntas sobre os cuidados pessoais para o informante:

*Qual é a sua estimativa da capacidade mental do doente nas seguintes áreas:

	Sem ajuda	Botões ocasionalmente mal abotoados, etc.	Sequência errada, peças frequentemente esquecidas	Incapaz de se vestir
A. Vestir-se (The Dementia Scale of Blessed)	0	1	2	3
	Sem ajuda	Necessita de instruções	Às vezes necessita de ajuda	Necessita sempre ou quase sempre de ajuda
B. Lavar-se, arranjar-se	0	1	2	3
	De forma limpa; talheres adequados	De forma desordenada; colher	Sólidos simples	Tem de ser alimentado
C. Hábitos alimentares	0	1	2	3
	Controlo completo normal	Às vezes urina na cama	Urina frequentemente na cama	Incontinência dupla (urina e fezes)
D. Controlo dos esfíncteres (The Dementia Scale of Blessed)	0	1	2	3

* Pode ser considerada a classificação de 1, se os cuidados pessoais do doente estiverem limitados face a um nível anterior, mesmo não recebendo instruções.

Questionário de Avaliação Clínica da Demência

Perguntas sobre a memória para o doente:

1. Tem problemas de memória ou raciocínio? ☐ Sim ☐ Não

2. Há poucos instantes, o seu (parceiro, etc.) contou-me um acontecimento que se passou recentemente. Quer contar-me o que aconteceu? (Se for necessário, obtenha pormenores tais como o local, hora, pessoas envolvidas, qual foi a duração, quando acabou e como o doente ou outras pessoas chegaram lá).

No espaço de 1 semana

1,0 – Correcto (em grande parte) _____

0,5 _____

0,0 – Incorrecto (em grande parte) _____

No espaço de 1 mês

1,0 – Correcto (em grande parte) _____

0,5 _____

0,0 – Incorrecto (em grande parte) _____

3. Vou dar-lhe um nome e um endereço para memorizar durante alguns minutos. Repita este nome e endereço: (Repita até a frase ser repetida correctamente ou até um máximo de três tentativas).

Elementos	1	2	3	4	5
	João	Borges,	Rua do Mercado,	42	Guimarães
	João	Borges,	Rua do Mercado,	42	Guimarães
	João	Borges,	Rua do Mercado,	42	Guimarães

(Sublinhe os elementos repetidos de forma correcta em cada uma das tentativas).

4. Quando nasceu? _____

5. Onde nasceu? _____

6. Qual foi a última escola que frequentou?

Nome _____

Cidade _____ Classe _____

7. Qual foi a sua ocupação/emprego principal (ou do seu parceiro, caso não tivesse emprego)? _____

8. Qual foi o seu último emprego principal (ou do seu parceiro, caso não tivesse emprego)? _____

9. Quando se reformou (ou o seu parceiro) e porquê? _____

10. Repita o nome e endereço que lhe pedi para memorizar:

Elementos	1	2	3	4	5
	João	Borges,	Rua do Mercado,	42	Guimarães

(Sublinhe os elementos repetidos correctamente).

Questionário de Avaliação Clínica da Demência

Perguntas sobre a orientação para o doente:

Registe literalmente a resposta do doente a cada pergunta

1. Qual é a data de hoje?

☐ Correcto ☐ Incorrecto

2. Qual é o dia da semana?

☐ Correcto ☐ Incorrecto

3. Qual é o mês?

☐ Correcto ☐ Incorrecto

4. Qual é o ano?

☐ Correcto ☐ Incorrecto

5. Qual é o nome deste local?

☐ Correcto ☐ Incorrecto

6. Em que terra nos encontramos?

☐ Correcto ☐ Incorrecto

7. Que horas são?

☐ Correcto ☐ Incorrecto

8. (Na sua opinião), o doente sabe quem é o informante?

☐ Correcto ☐ Incorrecto

Questionário de Avaliação Clínica da Demência

Perguntas sobre o discernimento e resolução de problemas para o doente:

Instruções: Caso a resposta inicial do doente não mereça uma avaliação de 0, insista no assunto para identificar o melhor entendimento do problema por parte do doente. Marque com um círculo a resposta que mais se aproxima.

Semelhanças:

Exemplo: “Em que aspecto se assemelha um lápis a uma caneta? (instrumentos de escrita)

Em que aspecto se assemelham estas coisas?” Resposta do doente

1. nabo.....couve-flor _____
(0 = vegetais)
(1 = alimentos comestíveis, seres vivos, podem ser cozinhados, etc.)
(2 = respostas não pertinentes; diferenças; compram-se)
2. escrivaninha.....estante de livros _____
(0 = mobiliário, mobiliário de escritório; ambos servem para guardar livros)
(1 = em madeira, pernas)
(2 = não pertinentes; diferenças)

Diferenças:

Exemplo: “Qual é a diferença entre açúcar e vinagre? (doce vs. azedo)

Qual é a diferença entre estas coisas?”

3. mentira.....erro _____
(0 = um é intencional, o outro não)
(1 = um é mau, o outro é bom – ou explica apenas um)
(2 = tudo o resto, semelhanças)
4. rio.....canal _____
(0 = natural - artificial)
(2 = tudo o resto)

Cálculos:

5. Quantas moedas de 5 cêntimos perfazem um euro? ☐ Correcto ☐ Incorrecto
6. Quantas moedas de 50 cêntimos perfazem 15,50 euros? ☐ Correcto ☐ Incorrecto
7. Subtraia 3 a 20 e continue a subtrair 3 a cada número novo até ao fim. ☐ Correcto ☐ Incorrecto

Discernimento:

8. Depois de chegar a uma cidade que não conhece, de que forma tentaria localizar um amigo que gostaria de visitar?

(0 = tentar a lista telefónica; telefonar a um amigo comum)
(1 = telefonar à polícia, telefonar para as Informações (normalmente não facultam endereços)
(2 = nenhuma resposta clara)
9. Avaliação do doente relativamente à sua incapacidade e posição na vida e a sua percepção das razões porque está presente neste exame (mesmo que já tenha avaliado este aspecto, classifique aqui):

☐ Bom discernimento ☐ Discernimento parcial ☐ Pouco discernimento

AValiação Clínica da Demência (CDR)

AValiação Clínica da Demência (CDR):	0	0,5	1	2	3
--------------------------------------	---	-----	---	---	---

	Limitação				
	Nenhuma 0	Suspeita 0,5	Ligeira 1	Moderada 2	Grave 3
Memória	Nenhuma perda de memória ou esquecimento ligeiro inconstante	Esquecimento ligeiro constante; recordação parcial dos acontecimentos; esquecimento "benigno"	Perda de memória moderada; mais acentuada nos acontecimentos recentes; interfere com as actividades do dia-a-dia	Perda de memória grave; apenas memorização de material retido com insistência; rápida perda de material novo	Perda de memória grave; restam apenas fragmentos
Orientação	Bem orientado	Bem orientado com ligeira dificuldade nas relações temporais	Dificuldade moderada nas relações temporais; orientado no espaço durante o exame; possível desorientação geográfica noutros locais	Dificuldade grave nas relações temporais; quase sempre desorientado no tempo, frequentemente no espaço	Orientado apenas em relação a si próprio
Discernimento e resolução de problemas	Resolve problemas do dia-a-dia, lida bem com actividades financeiras e de negócio; bom discernimento em relação a desempenhos no passado	Ligeira limitação para resolver problemas, semelhanças e diferenças	Dificuldades moderadas para resolver problemas, semelhanças e diferenças; normalmente mantém o discernimento social	Limitação grave para resolver problemas, semelhanças e diferenças; normalmente o discernimento social é limitado	Incapacidade de discernimento ou resolução de problemas
Relacionamento com a comunidade	Funcionamento independente ao nível habitual no trabalho, compras, grupos de voluntariado e outros	Ligeira limitação nestas actividades	Incapaz de funcionar independentemente nestas actividades, embora, de certa forma, ainda possa estar envolvido; numa avaliação superficial aparenta normalidade	Incapacidade de funcionamento independente fora de casa Aparenta estar suficientemente bem para realizar funções fora de casa	Aparenta estar demasiado doente para realizar funções fora de casa
Casa e passatempos	Vida em casa, passatempos e interesses intelectuais bem preservados	Vida em casa, passatempos e interesses intelectuais ligeiramente limitados	Limitação ligeira, mas evidente, do funcionamento em casa; abandono das tarefas mais difíceis; abandono dos passatempos e interesses mais complicados	Preservado apenas o interesse nas tarefas simples; interesses muito restritos e fracos	Nenhuma capacidade significativa de realizar funções em casa
Cuidados pessoais	Inteiramente capaz de cuidar de si próprio		Necessita de instruções	Necessita de ajuda para se vestir, para a higiene e para manter objectos pessoais	Necessita de muita ajuda com os cuidados pessoais; incontinência frequente

Classifique apenas como declínio face ao nível habitual anterior devido a perda cognitiva, não devido a limitação resultante de outros factores.

ATTACHEMENT
(8.c)

MINI-MENTAL STATE EXAME

NOME: _____

IDADE: _____ ANOS

DATA: _____ de _____ de _____

1. ORIENTAÇÃO (1 ponto por cada resposta correcta).

Em que ano estamos? _____
Em que mês estamos? _____
Em que dia do mês estamos? _____
Em que dia da semana estamos? _____
Em que estação do ano estamos? _____
Em que país estamos? _____
Em que distrito vive? _____
Em que terra vive? _____
Em que casa estamos? _____
Em que andar estamos? _____

NOTA:

2. RETENÇÃO (contar 1 ponto por cada palavra correctamente repetida).

“Vou dizer três palavras; queria que as repetisse, mas só depois de eu as dizer todas; procure ficar a sabê-las de cór”.

Pêra _____
Gato _____
Bola _____

NOTA:

3. ATENÇÃO E CÁLCULO (1 ponto por cada resposta correcta. Se der uma errada mas depois continuar a subtrair bem, consideram-se as seguintes como correctas. Parar ao fim de 5 respostas.)

“Agora peço-lhe que me diga quantos são 30 menos 3 e depois ao número encontrado volta a tirar 3 e repete assim até eu lhe dizer para parar”.

27 ____ 24 ____ 21 ____ 18 ____ 15 ____

NOTA:

4. EVOCAÇÃO (1 ponto por cada resposta correcta).

“Veja se consegue dizer as três palavras que pedi há pouco para decorar”.

Pêra _____
Gato _____
Bola _____

NOTA:

5. LINGUAGEM (1 ponto por cada resposta correcta)

a. “Como se chama isto? Mostrar objectos:

Relógio _____
Lápis _____

NOTA:

b. “Repita a frase que eu vou dizer: O RATO ROEU A ROLHA”

NOTA:

c. “Quando eu lhe der esta folha de papel, pegue nela com a mão direita, dobre-a ao meio e coloque-a no chão”, (ou “sobre a cama”, se for o caso); dar a folha segurando com as duas mãos.

Pega com a mão direita _____
Dobra ao meio _____
Coloca no chão _____

NOTA:

d. “Leia o que está neste cartão e faça o que lá diz”. Mostrar um cartão com a frase bem legível, “FECHE OS OLHOS” sendo analfabeto ler-se a frase.

Fechou os olhos

NOTA:

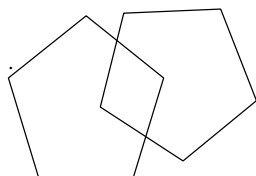
e. “Escreva uma frase inteira aqui”. Deve ter sujeito e verbo e fazer sentido; os erros gramaticais não prejudicam a pontuação.

NOTA:

6. HABILIDADE CONSTRUTIVA (1 ponto pela cópia correcta)

Deve copiar um desenho. Dois pentágonos parcialmente sobrepostos; cada um deve ficar com 5 lados, dois dos quais intersectados. Não valorizar tremor ou rotação.

DESENHO



CÓPIA

(Máximo 30 pontos)

TOTAL:

FECHE OS OLHOS

ATTACHEMENT
(8.d)

ESCALA DE QUEIXAS SUBJECTIVAS DE MEMÓRIA (QSM)

1. *Tem queixas acerca da sua memória?*
0 – Não
1 – Sim, mas sem importância
2 – Sim, com alguma importância
3 – Sim, com problemas
2. *Já lhe disseram que o(a) acham esquecido(a)?*
0 – Não
1 – Sim, por vezes
2 – Sim, frequentemente
3. *Esquece com frequência nomes de pessoas da família ou de amigos?*
0 – Não
1 – Sim, mas sem importância
2 – Sim, com alguma importância
3 – Sim, com problemas
4. *Esquece-se frequentemente onde põe as coisas?*
0 – Não
1 – Sim, mas sem importância
2 – Sim, com alguma importância
3 – Sim, com problemas
5. *Costuma tomar apontamentos para não se esquecer das coisas?*
0 – Não
1 – Sim, por vezes
2 – sim, frequentemente
6. *A conversar costuma ter dificuldades em encontrar as palavras?*
0 – Não
1 – Sim
7. *Já alguma vez se perdeu perto de sua casa?*
0 – Não
1 – Sim
8. *Acha que anda a pensar mais devagar do que antes?*
0 – Não
1 – Sim
2 – Sim, com problemas
9. *Sente que as suas ideias por vezes ficam confusas (baralhadas)?*
0 – Não
1 – Sim
2 – Sim, com problemas


10. Tem tido dificuldades em concentrar-se?


0 – Não

1 – Sim

2 – Sim, com problemas

Total: _____

 Auto-aplicação

 Hetero-aplicação. Motivo? _____